Actiq®

"Master Plan"

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Coordinated by Martha Arnold

November 16, 2000

PLAINTIFFS TRIAL EXHIBIT
P-25249_00001

Actiq® Master Plan Table of Contents

1.0 Executive Summary

Actiq® (oral transmucosal fentanyl citrate) was launched in April 1999 by Abbott Hospital Products Division. Initial wholesaler stocking exceeded the sell-in forecast, however, it soon became apparent that retail pharmacy stocking and initial sales pull through were far below forecast. The product sales launch seemed to be underfunded and poorly executed.

In March 2000, Anesta re-acquired the rights to *Actiq*, and set about re-launching the product. Increased funding, a larger sales force and better execution has fueled growth and *Actiq* hit forecast through August. Since then, however, the product is beginning to fall short of expectations as reflected in the 2000 forecast. With Cephalon's acquisition of the business, it is time to critically review the business model and change it where necessary to build the *Actiq* business to its potential.

Lessons Learned

1. *Actiq* has a multitude of advantages, including superior performance and strong patient preference. Physicians frequently understand the theoretical benefits of the product quite quickly—the issue has been gaining trial of the product, experiencing the benefits through their own patients, and firmly establishing *Actiq* in their prescribing practices. At this point, communication of some *Actiq* advantages are anecdotal, as lack of clinical data specific to the product's core benefit messages (speed of onset and patient preference, for example) and heavy handed regulatory oversight has significantly limited the messages that can be promoted.

2. *Actiq* is a very challenging product to write and physicians have to be highly motivated to do so. The "hassle factor" for using *Actiq* is high, and all of the factors outlined below contribute.

   - The educational requirements associated with a new dosage form and (in many cases) new indication are significant and very time consuming. This relates to the time spent educating physician and staff, and the time spent by them educating the patient.
   - Retail product availability is weak, and is frequently cited as a barrier to continued usage. Abbott has experienced difficulties making and keeping adequate inventories across their distribution centers, leading to unacceptable delays in getting the product through the wholesaler to retail. Also, as *Actiq* is growing at a very rapid rate and wholesaler ordering systems tend to be electronic and historically-based, wholesalers are frequently out of stock on at least several of the six strengths that are available.
   - The cost is high compared to competition.
   - The titration process is perceived to be tedious, and for many new users, it truly is. Most of these physicians are accustomed to using an equi-analgesic chart to switch between opioids or a simple percentage of the ATC dose to determine the breakthrough pain dose, and *Actiq* doesn't fit into this approach.

   All of these factors are exacerbated by the fact that many breakthrough cancer patients are terminally ill. The investment in education and obtaining supply needs to be repeated for each

new patient. These factors all contribute to the difficulty we've had in getting physicians to continue to write the product after an initial trial.

3. The number of physicians who have gotten over these barriers is relatively modest. In August retail outlet audit data, we identified about 576 writers (There are probably an additional 20% that are institutionally-based and therefore not captured in this data). The number of writers continues to grow, but is considerably smaller than had been forecast. The number of physicians writing for the first time grew significantly in July and August (following the introduction of the field sales organization in May), suggesting that a sustained promotional effort will likely address this issue.

4. Feedback from the field indicates that oncologists simply aren't treating that many people for breakthrough cancer pain, or aren't using strong opioids to treat breakthrough pain. According to the information in the literature, this number should be about 30% of all patients with active cancer (representing 67% of the 50% of patients with an active cancer diagnosis who have chronic cancer pain).

   We believe this disconnect is due in part to patient satisfaction with their current therapy. When converting patients to long acting opioids, many physicians continue using the previous therapy (typically a combination product such as Vicodin or Percocet) for breakthrough pain. These products will provide satisfactory relief for many patients. It frequently takes trial and experience with *Actiq* for patients and their physicians to realize the benefits *Actiq* provides. Another potential contributor is the simple undertreatment of cancer pain in general, with the resultant less aggressive use of opioid medications.

   The limitations of focusing on oncology as an opportunity has been tested to a degree by our Phase IV trial (AC 600/006). There, we've seen slower than anticipated enrollment in a study that was designed to test *Actiq* performance in a "real world" environment.

5. Among those physicians who are prescribing *Actiq*, activity is skewing increasingly towards the non-Oncologist. Units written by oncologists now represent just 16% of total product usage, with 48% coming from pain management specialists. This differential in opioid productivity is borne out by looking at the prescribing activity across all short acting opioids between our two target specialties, where top writing pain management specialists write +67% more scripts a month than do oncologists.

6. We believe that the pain management specialist is likely to be a more aggressive writer and a rapid adopter of *Actiq*. The pain physicians' patients tend to have difficult pain conditions that require *Actiq*'s potency and rapid onset. Further, the physicians treating pain full time are believed to be more open to new delivery systems and more comfortable fentanyl as an active ingredient. In addition, from a business perspective, these physicians tend to have patients who are more likely to be truly chronic, with many years of potential usage of the product, either for breakthrough pain or more generally for other chronic pain conditions.

Strategic Recommendations

Based on our experience to date with *Actiq*, we believe it can continue to grow aggressively into 2001 and beyond by expanding the target physician and patient population to allow penetration of the broad chronic pain market. This should be the driver of all activities associated with *Actiq* in 2001 – marketing, clinical, regulatory and operations.

Strategy recommendations that will impact the business over the next 18 to 24 months include:

- Expand the called on universe to expand the physician base, enrich the mix of pain specialists, while continuing the efforts to strengthen marketing programs:
  - Relaunch and reposition the product during 1Q01
  - Enhance field resources by redeveloping the organizations as Cephalon employees
  - Integrate non-personal promotional efforts (such as journal advertising and website based promotion).
  - Address logistical issues and implement labeling changes to make *Actiq* easier to write
  - Increase retail and wholesaler distribution and product pipeline
  - Continue aggressive peer to peer selling programs through medical education

- Develop and implement a regulatory strategy to "level the playing field" and obtain fair treatment for *Actiq* in comparison to competitors. Revisit the RMP and submit a sNDA to relax selected provisions that can help from a marketing perspective without reducing barriers to generics.

- Bring existing clinical programs to fruition and expand them to support broadened product usage
  - Generate and submit clinical data to amend the label to 1) simplify titration and 2) permit clearer communication of *Actiq*'s competitive advantages by amending the onset data and adding in appropriate comparative data (MSIR trial).
  - Invest in clinical program to broaden clinical database into non malignant chronic pain states. These will be mostly IND studies. We envision trials in breakthrough pain as well as more general chronic pain.
  - Publish and use these data in the short term for use in peer to peer environments and under WLF.

- Implement Third Party logistics program to obtain better control of distribution and address wholesaler availability issues.

Strategy recommendations that should be undertaken immediately, but will have longer term impact on the business include:

- File SNDA to move production from Abbott to Salt Lake City to create significant cost savings and control of manufacturing process. This should be approved by October 1, 2001

to meet our commitments to Abbott under the existing supply agreement

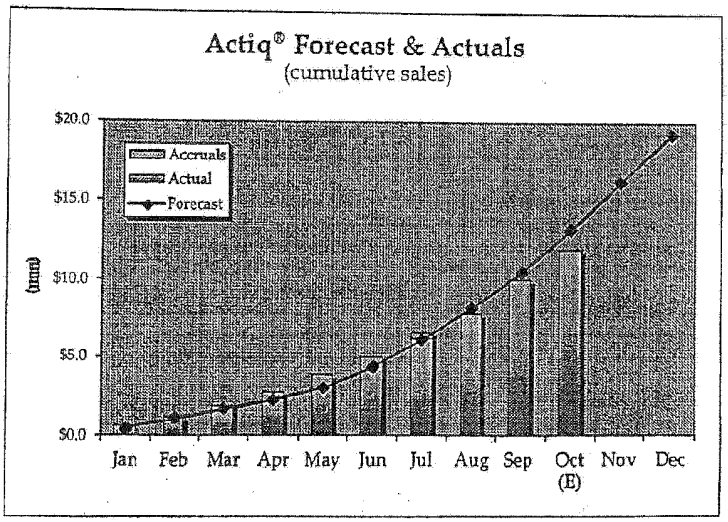
- Convene a multifunctional effort to evaluate the potential for *Actiq* in acute pain, taking into account competitive pipeline products, payor trends, and existing knowledge about *Actiq* characteristics and clinical results in opioid naïve subjects. Evaluate the role for the Fentanyl Oralet NDA as part of this effort.

- Continue efforts to effectively extend the *Actiq* exclusivity period through patent, trademark and copyright strategy. Evaluate any proposed changes to the Risk Management Program against potential reduction in barriers to entry by potential competitors.

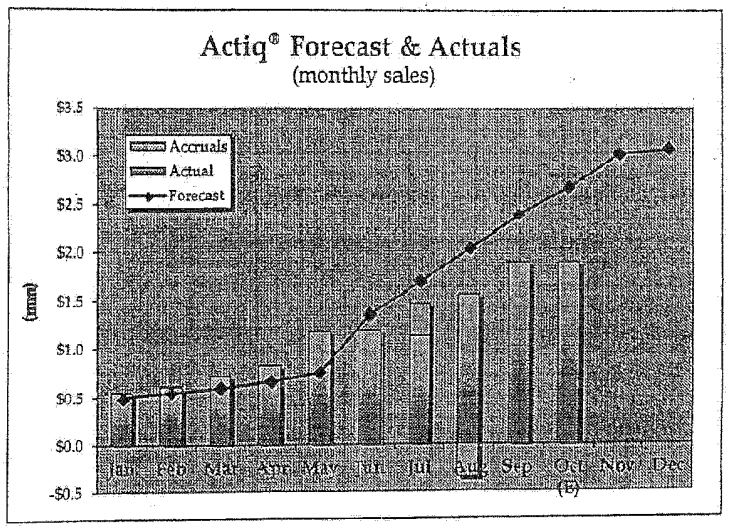
2.0 State of the Business

2.1 Situational Analysis
&
Current Performance

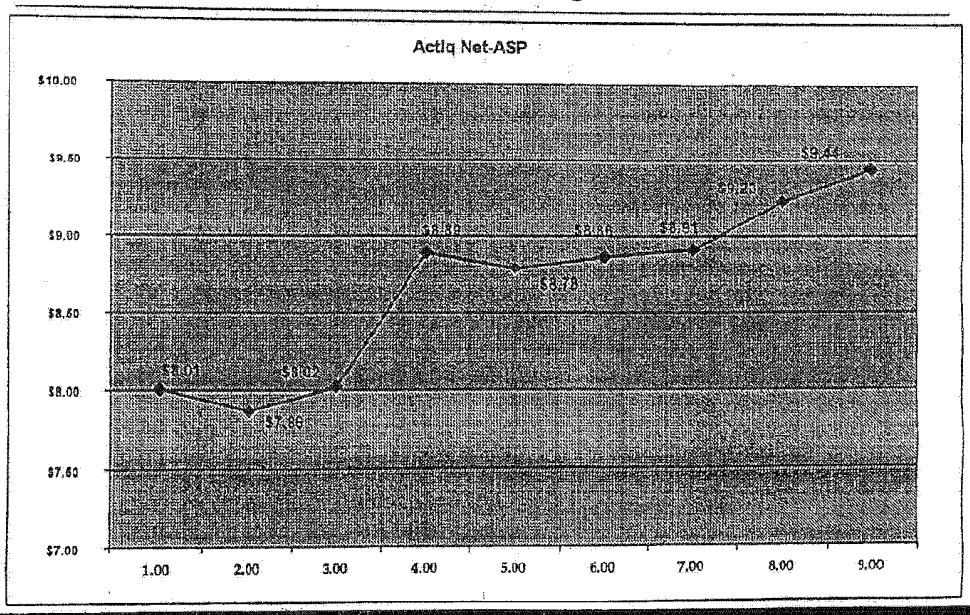
Actiq Sales
cumulative through October estimate



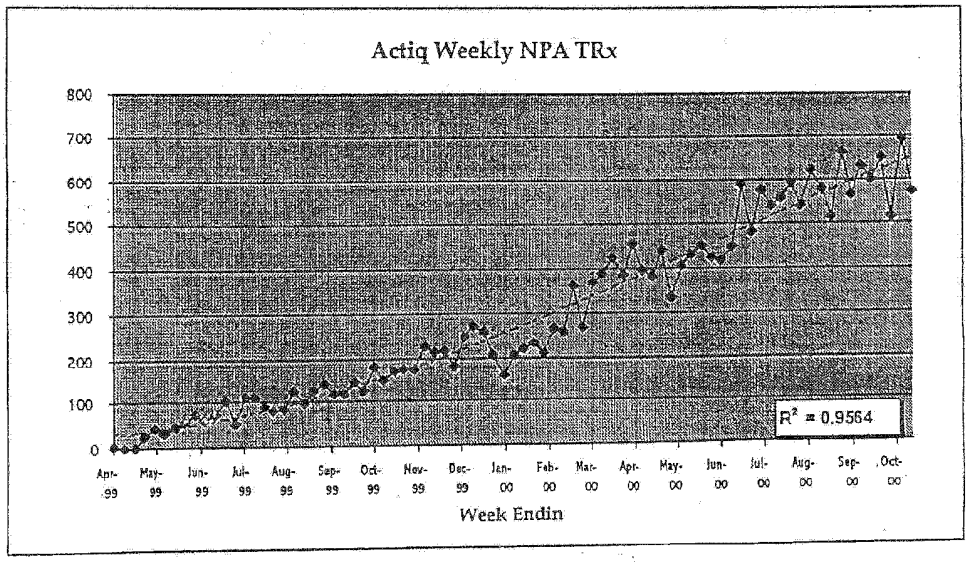
Actiq Sales
monthly through October estimate



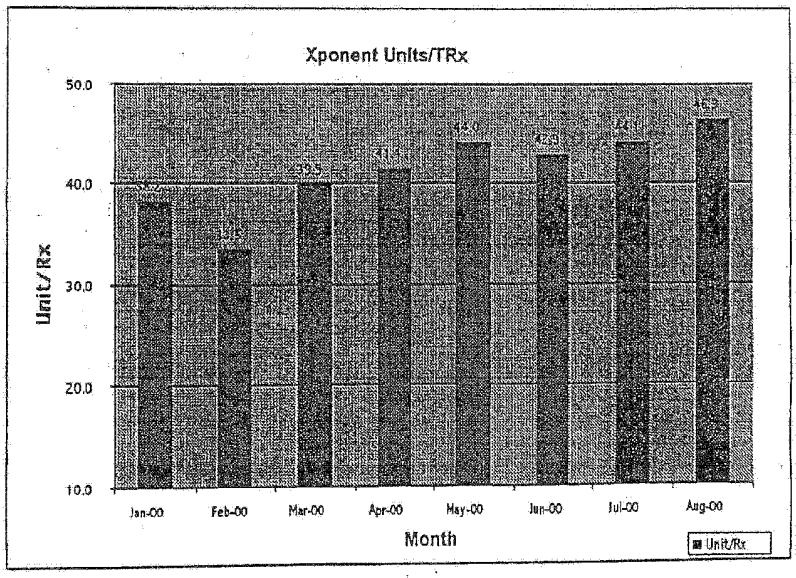
Actiq Sales
Factory Average Net Selling Price



Actiq Prescription Trends
IMS - Weekly NPA

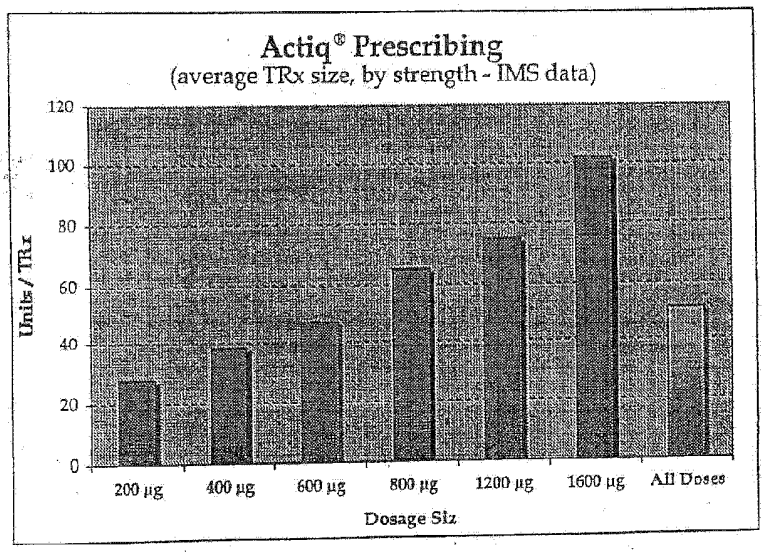


Actiq Prescriber Analysis
Xponent Units/Rx

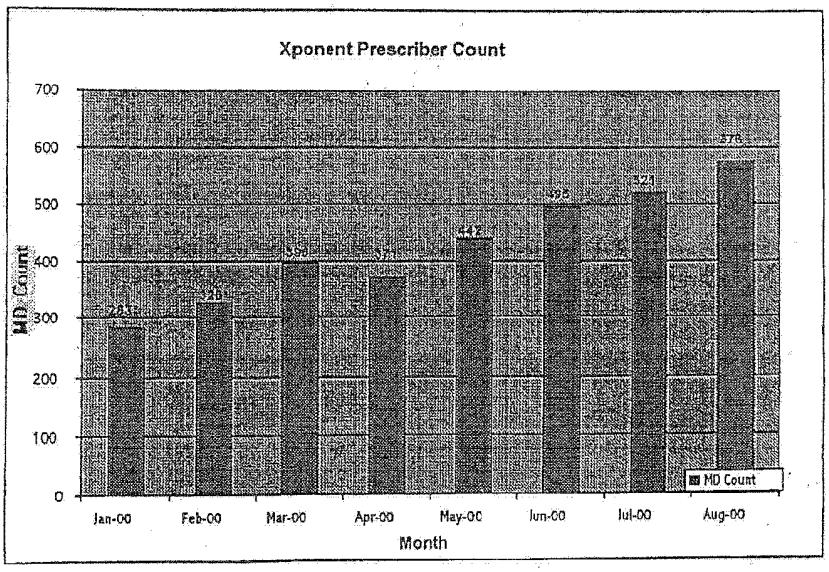


ANESTA

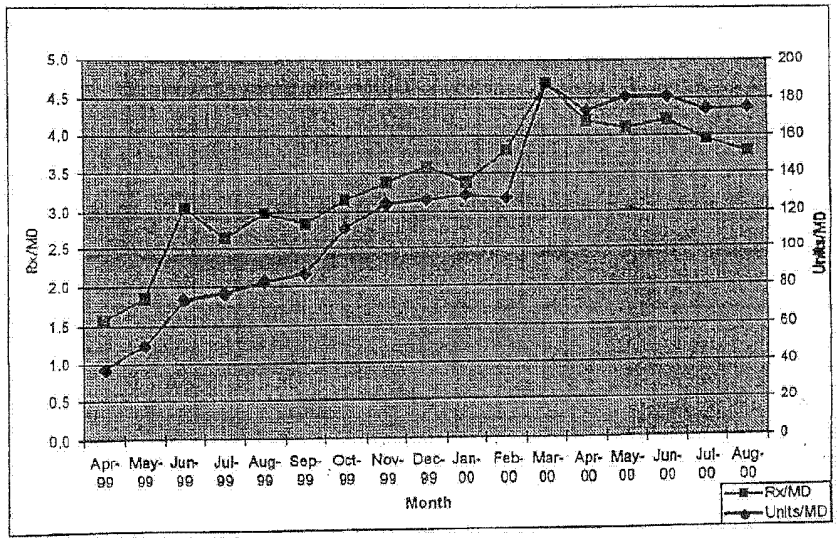
Actiq Prescriptions
prescription size by dosage strength - August



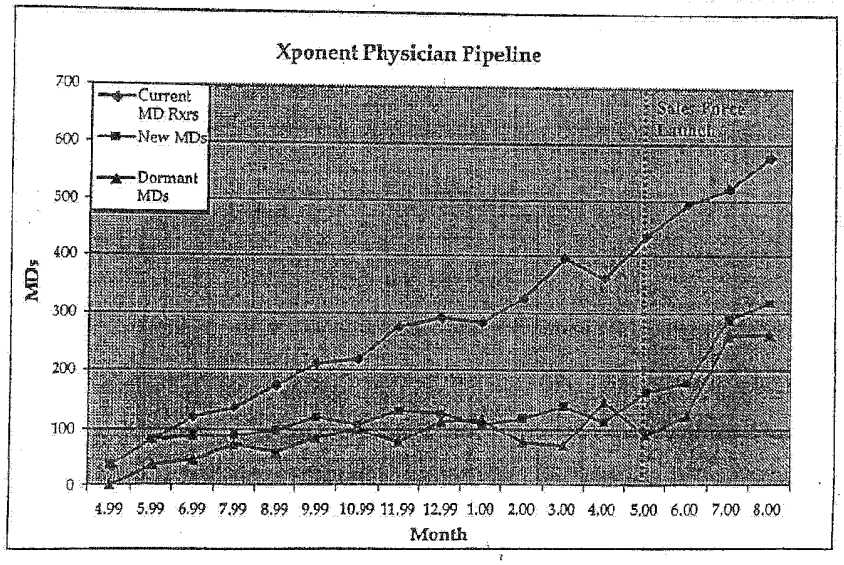
Actiq Prescriber Analysis
Monthly Xponent Prescribers



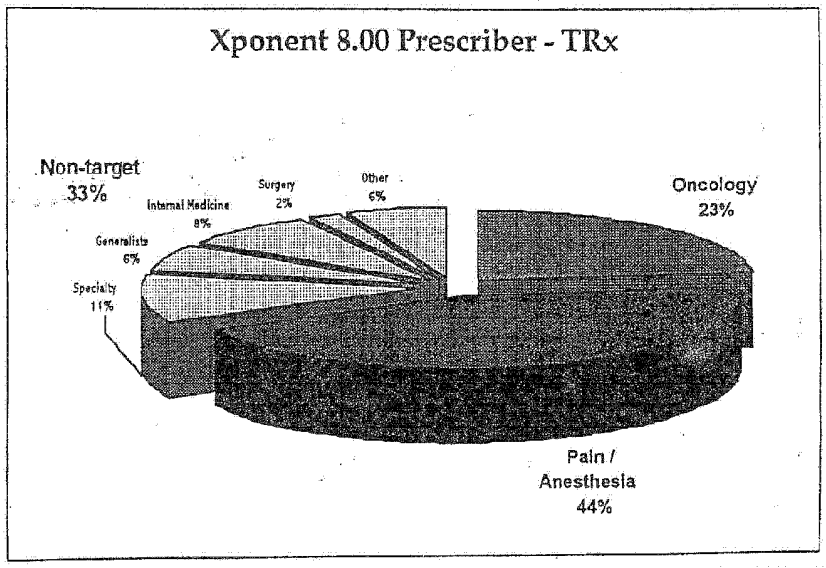
Actiq Prescriber Analysis
Xponent TRx/MD & Units/MD



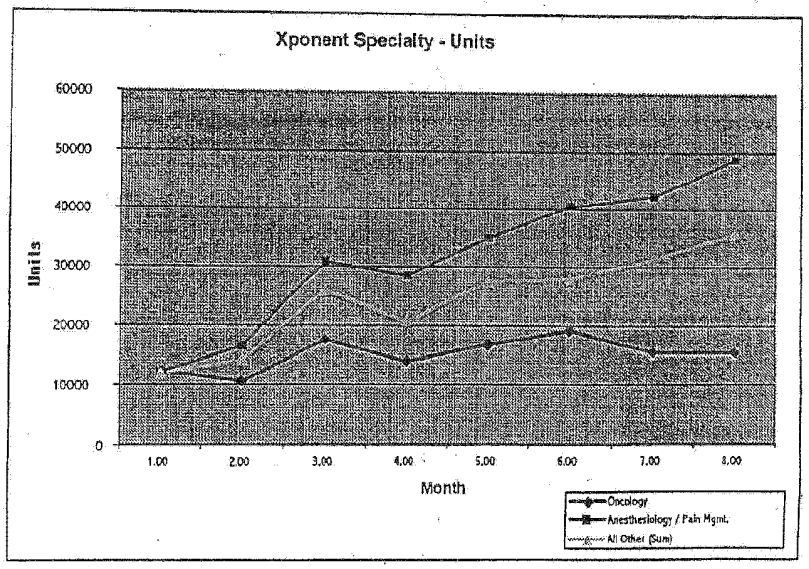
Actiq Prescriber Analysis
Xponent Physician Pipeline



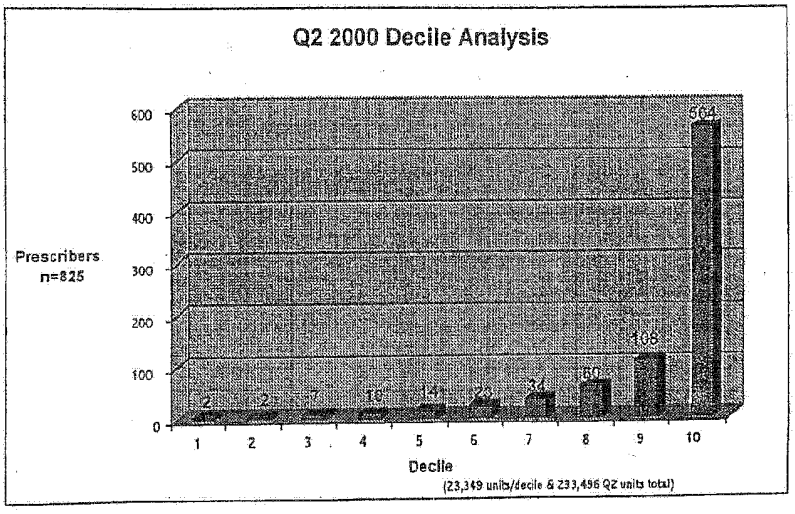
Actiq Prescriber Analysis
Xponent - August Scripts



Actiq Prescriber Analysis
Xponent Units by Specialty



Actiq Decile Analysis
Xponent Physician Prescribers



2.2 Competition

The prescription opioid market can be classified into two broad categories of drugs:

- Short Acting Opioids
- Long Acting Opioids

Short acting opioids are commonly used in opioid naïve patients, who are experiencing acute pain episodes related to an injury, or surgery. As implied in the name their analgesic effect is short in duration, usually 2-6 hours.

Long acting opioids are commonly prescribed for opioid tolerant patients who have pain of a chronic nature, which is loosely defined as pain that has lasted anywhere from 6 weeks to 6 months; chronic non-malignant pain can exist for years. These drugs are often dosed on a 12-24-48-72 hour interval.

Breakthrough pain is a bit of a hybrid condition, as by definition, it can only occur in patients who are being treated with long acting analgesics for the baseline component of their chronic pain. Breakthrough pain was first described in 1990, and is becoming increasingly well known such that the standard of care is now to prescribe a short acting pain medication at the same time as the long acting medication is initiated. Of note, there is a theoretical preference to use the same active opioid ingredient in both medications. This philosophy has been aggressively promoted by the companies that have had short and long acting versions of selected active ingredients.

The WHO Ladder

Opioids are classified based on their potency and DEA schedule and their fit into the World Health Organizations (WHO) Three-Step Analgesic Ladder. The WHO ladder system is segmented by the degree of pain; mild to moderate, moderate to severe, and severe. The ladder matches the degree of pain to the potency of the medication, and anticipates the need for stronger medications to control pain at each step. Adjuvant drugs are also used at each step of the WHO ladder to enhance the analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, and provide independent analgesia for specific types of pain. Examples of these medications are corticosteroids, anticonvulsants, antidepressants, neuroleptics, antihistamines, and psychostimulants

- Step 1 of the WHO ladder contains Non-Opioids. Adjuvant medications may also be prescribed. Examples: Aleve®, Motrin®, Tylenol®, Ultram®. and Celabrex

- Step 2 of the WHO ladder contains Opioids for mild to moderate pain in combination with non-opioid analgesics (typically acetaminophen or NSAIDs). Adjuvant medications may also be prescribed. .Examples: Percocet®, Vicodin®, Tylenol w/codeine®

- Step 3 of the WHO ladder contains pure opioids for moderate to severe pain. Nonopioid analgesics and adjuvants may also be prescribed. Examples: MS Contin, Duragesic®, Oxycontin®, and Dilaudid®

Competitive Companies

There are relatively few major players in the opioid marketplace: Purdue Frederick, Janssen, Knoll, and Roxane are the largest. The primary focus for these companies has been on developing the outpatient chronic pain market for long acting, sustained release products. These products are positioned for both cancer and non-malignant chronic pain with duration of action between 12-72 hours. Many of these products also have short acting versions that until recently were promoted for acute pain, but which are now being promoted for "breakthrough pain".

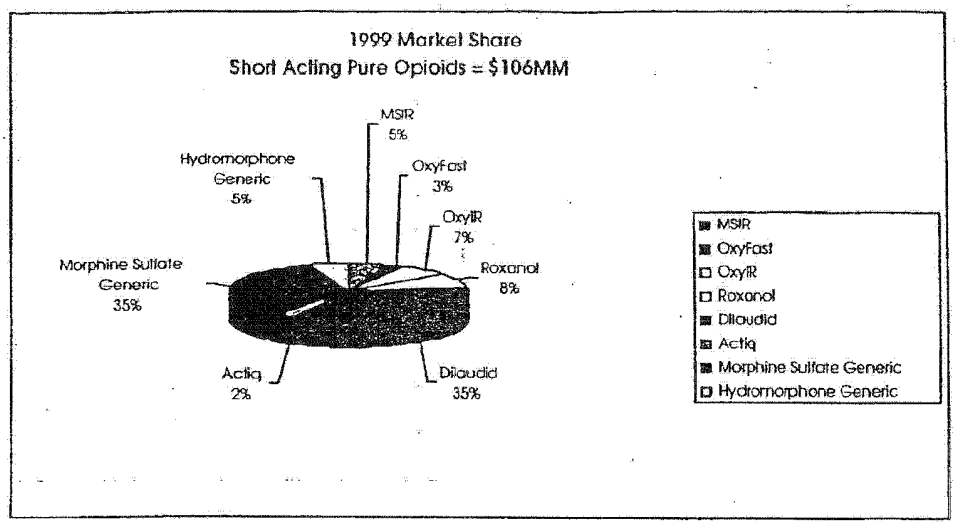
New product activity in the Step 3 pure opioid class has driven the market for ATC (Around the clock) and short acting medications to well over 1.2 billion dollars annually. In addition to the pure opioid agents listed below, there are many combination short acting opioids plus acetaminophen products available in Step 2 of the WHO Ladder with a total market of 1.1 billion dollars yearly as well.

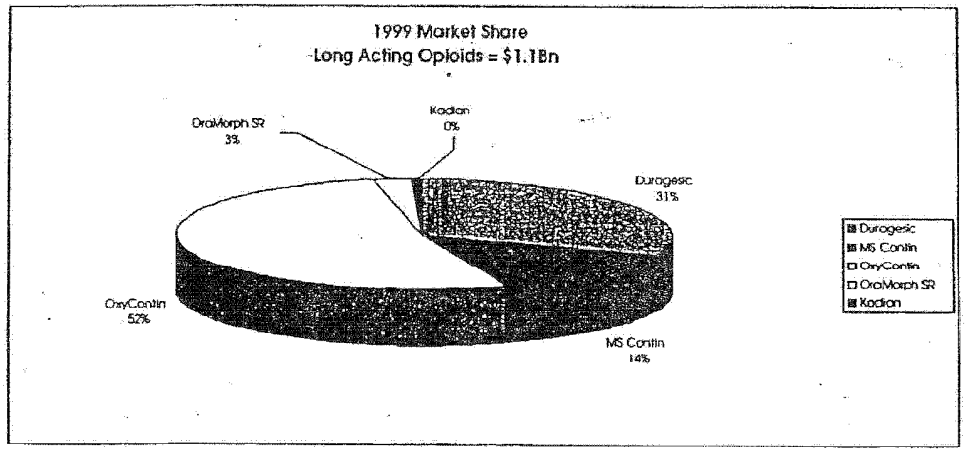
SHORT-ACTING PURE OPIOIDS

Trade Name	**Generic Name**	**Manufacturer**
Actiq	Transmucosal Fentanyl	Cephalon
Roxanol MSIR	Morphine Sulfate	Roxane Purdue
Dilaudid	Hydromorphone HCL	Knoll
Oxy IR Oxyfast	Oxycondone	Purdue
Generic Morphine Generic Hydromorphone	Morphine Sulfate Hydromorphone HCL	Various Companies

LONG-ACTING OPIOIDS

MS Contin Oramorph	Morphine Sulfate	Purdue Roxane
Kadian	Morphine Sulfate	Faulding
Oxycontin	Oxycodone	Purdue
Duragesic	Transdermal Fentanyl	Janssen





Purdue Frederick -- Purdue is by far the strongest company in this group and is becoming increasingly dominant. A very aggressive, privately held company with very deep pockets, the Purdue sales force numbers approximately 1000 representatives across the country. Purdue has been very active in the implementation of the JCAHO standards on pain at the institutional level.

MS Contin (sustained release morphine) was the first of the long acting medications and peaked with sales of $157MM in 1999, 2000 sales are trending downwards and are estimated

at $147MM. The Purdue companion short acting product MSIR had sales of $6MM in 1999 and the other short acting generic morphine products had sales of $36.8MM in 1999. The total short acting opioid market had sales of $106MM in 1999. Purdue has aggressively switched their promotion efforts from MSContin/MSIR, which has lost share to the generics over to OxyContin/Oxy IR & Oxyfast where they have stronger patent protection.

OxyContin in a sustained release oxycodone formulation of oxycodone. When partnered with OxyIR and OxyFast as immediate release or short acting formulations, oxycodone represents Purdue's largest product with combined 1999 sales of approximately $610MM. OxyContin was launched approximately 4 years ago, and has been aggressively promoted across all major opioid-writing specialties, with an expanding usage among surgeons for post operative and other acute pain states. Purdue has aggressively captured business by trading patients up from short-acting fixed combinations like Percocet by effectively positioning OxyContin as a non-morphine alternative that is effective for moderate to severe pain of all types, both acute and chronic.

In terms of new products, Purdue is currently waiting FDA approval for a sustained release version of hydromorphone (the short acting version is called Dilaudid and it is marketed by Knoll) brand named "Palladone XL". It is our understanding that they have run into some hurdles with the FDA and have pulled back pre-approval promotion of this product. Given the very strong efficacy impression associated with Dilaudid, we believe that Purdue may position Palladone for severe pain and OxyContin for moderate to severe pain. This strategy will allow them to dominate the entire moderate to severe; short to long acting marketplace, with unassailable leadership positions in the high volume, high margin sustained release orals segment across all active ingredients.

Janssen – Janssen markets fentanyl in a long acting transdermal patch delivery system called Duragesic. 1999 IMS sales were estimated at $353 million (company info shows closer to $500MM worldwide) with the bulk of these dollars coming from usage in non-malignant pain. Ortho-Biotech (a sister Johnson &Johnson Company) sells Duragesic along with their product Procrit for fatigue to office-based Oncologists. Janssen markets Duragesic in hospital cancer centers and pain clinics using their hospital sales force, which numbers about 100 people. In addition, Janssen calls on hospices and long term care facilities using a long-term care sales force and a co-promotion agreement with Alza, the developer and manufacturer of the patch. Janssen also has a primary care sales force that promotes Duragesic for chronic non-malignant pain. In total J&J has approximately 800-1000 representatives promoting Duragesic to the high writers of opioids across all specialties.

Duragesic faced a number of similar issues that *Actiq* is facing in the early years of its launch. It was a novel delivery system that was relatively expensive and there was confusion over the dosing. Further, Duragesic was associated with several deaths resulting from inappropriate physician prescribing. It was also hampered by not having a short acting oral fentanyl that physicians could use to titrate the long acting Duragesic .

Because of the current dogma about using the same short acting and long acting opioid there appears to be natural synergy between *Actiq* and Duragesic. That said, we have been told that Janssen's management has instructed their representatives not to discuss *Actiq*. We suspect that this traces to a wariness associated with Abbott's co-promotion agreement on OxyContin and the fact that they want their representatives focused on selling their own drug. Despite this attitude at the national level, a number of our representatives have worked with their local Janssen or OrthoBiotech reps to do joint programs or to gain access to offices. In addition, we share many speakers in common, and find that many Janssen speakers include *Actiq* in their presentations. That said, we have not approached Janssen officially about conducting joint programs.

Alza/Janssen have been working on a new patch technology that uses a push button mechanism to deliver fentanyl via an electrical charge rapidly across the skin for BTP, while at the same time providing a controlled release delivery for chronic pain. This system is called e-trans, and it is our understanding that progress has been quite slow. Alza just announced that it had entered into Phase III studies for acute pain.

Other players: – Knoll, and Roxane are second tier pain companies marketing various versions of oxycodone, hydromorphone, and morphine with and without nonopioids in combination. These companies have relatively small sales forces in comparison to Purdue and Janssen. of morphine and hydromorphone

Knoll markets several significant combination products including Vicodin and Vicoprofen (the latter of which they co-promote with Abbott) for moderate pain and Dilaudid for severe pain. Dilaudid is aggressively positioned as having a rapid onset of action, potent efficacy and a flexibility across dosage forms that supports a "spectrum of pain relief" positioning. Dilaudid is perceived to be both fast and strong, attributes which fit nicely with treating BTP. 1999 sales for Dilaudid were 37M.

Roxane markets a range of palliative care products, including Roxanol (morphine liquid) Oramorph SR (sustained release morphine) and Roxicodone (oxycodone) in oral, injectable and suppository forms. Roxane has aggressively sought out the cancer and palliative care/ hospice market, but has had limited success going head to head with Purdue in analgesics.

In addition to these companies there are a number of generic manufacturers such as Forrest, Faulding, Endo, UCB and others which all have generic versions of one form or another of morphine oxycodone, or hydrocodone alone or in combination with acetaminophen. The marketing efforts behind these products are relatively small in comparison to the major pain companies.

3.0 Marketing/Commercial

3.1 Current *Actiq* SWOT Summary

Strengths	Weaknesses
1. Clinical performance as a rapid acting, effective on demand pain reliever 2. Uniqueness of indication 3. Extensive clinical database 4. Large base of published product literature 5. Anecdotal, positive impact on Quality of Life 6. Well known and accepted active drug - fentanyl	7. Limited availability at retail pharmacies 8. Value proposition not well communicated 9. Lack of a meaningful, focused positioning and message 10. High price combined with limited/weak outpatient drug coverage for Medicare patients 11. No equi-analgesic dosing 12. Perceived tedious titration process 13. Perceived safety risk for children 14. Narrow Indication combined with lack of protection from similar claims by competitors 15. Opioid tolerant requirement, limits drug selection as initial therapy
Opportunities	**Threats**
• Increased share of voice (both personal and non-personal selling) • Demystifying and simplifying titration ✓ Peer to peer teaching ✓ 400mcg to start ✓ labeling adjustments to support 400 – 800 – 1600 progression • Passion among a relatively small number of key physicians • Supporting the "patient and professional journey" by an integrated and supportive logistics program • Anecdotal, but positive impact on Quality of Life • Repositioning and restage during 1Q01 • Indication expansion (longer term) • Effective expansion of indication via WLF • Relaxation of regulatory constraints	16. Competitively, we will always be out manned, outspent 17. Competitive products making claims for BTCP without having done any work 18. Continued subpart H classification 19. Development of capitation-based drug benefits at the physician level 20. Accidental use resulting in death by children, or opioid naïve patients

3.2 Marketing and Promotion

Actiq promotional programs have the broad strategic objectives of generating product trial, seeing trial through to a successful experience, and building a stronger, broader base of prescribing physicians to generate future sustainable *Actiq* growth.

Specific areas of focus in 2000 and into 2001 include programs designed to:

3.2.1 Relaunch *Actiq* with strengthened positioning and messaging.

3.2.2 Enhance field presence to expand reach and improve frequency and quality of contact. Evaluate non-personal selling and promotion to complement sales force activities and implement as appropriate.

3.2.3 Address logistical issues via an integrated, single point of contact and a focused effort to improve wholesale and retail availability.

3.2.4 Utilize peer to peer influence opportunities to overcome prescribing objections.

3.2.1 Develop and Relaunch the Product with Strengthened Positioning and Messaging

A key activity for *Actiq* 2000 has been to develop a stronger brand and more meaningful, focused positioning for *Actiq* and to execute that strategy creatively to support the relaunch of the product. These new elements will be rolled out at the February national sales meeting.

Anesta retained Gerbig, Snell / Weisheimer & Associates, Inc. (GSW) as Agency of Record for *Actiq*. In this role, GSW is our strategic and tactical executional partner in the development of promotional and advertising programs for *Actiq*.

Repositioning / Relaunch

Even before re-acquiring the rights to *Actiq*, it was obvious that the iceberg branding and positioning execution chosen by Abbott was ineffective. An analysis by GSW concluded that the current positioning and materials:

- had not provided a clinically-meaningful reason to prescribe *Actiq*
- had not communicated the value proposition well. (A "value proposition" is a motivating reason for someone to choose *Actiq*. It answers the question of "what does this product bring to the marketplace that is more valuable than what's been previously available?").
- had been unemotional in approach in a marketplace that lends itself to emotional appeal

The branding and positioning campaign began in April 2000 and will soon be completed, with a presentation and review of the relaunch sales aid on November 7 at Cephalon.

The brand and agency have been working diligently on this process, working through four rounds of market research: attribute, positioning, concept, and message flow.

21. Attribute testing results showed that the dual benefits of rapid relief of pain (within 15 minutes) and patient preference versus other products were the most compelling attributes

22. "*Actiq*'s rapid onset of action relieves breakthrough cancer pain faster than any other product" is the chosen positioning statement.

23. The "Polaroid" concept was confirmed as the concept that best conveyed the new *Actiq* brand and positioning.

7. Core messages were tested to determine the key strategic messages and flow for the sales aid and supporting promotional materials. The key communication points identified in testing include:

   - ✓ Rapid onset of action
   - ✓ Duration of action matched to a BTCP episode
   - ✓ Minimal side effects
   - ✓ Simple, noninvasive administration
   - ✓ The speed and power of fentanyl
   - ✓ Patient preference
   - ✓ Proprietary design
   - ✓ Oral transmucosal delivery

   In addition, background on breakthrough pain needs to be provided to establish that it is a "must treat" condition due to its rapid onset, severity, and unpredictability and because it is not as readily understood or treated as persistent (underlying) cancer pain

A branded sales aid is in development and will be presented at Cephalon on November 7. The relaunch sales aid will be introduced to the sales force at the February 2001 meeting for immediate use thereafter.

The relaunch sales aid will not be a leave-behind and will, therefore, be augmented by a number of branded support materials for distribution. These include:

- Topic specific leave behinds (efficacy, BTCP, safety)
- Dosing/titration guide
- *Actiq* Answers sales aid/rolodex card/magnet
- Patient education tear sheet

We recommend conducting market research in the fourth quarter of 2001 to gauge effectiveness of the relaunch campaign and making adjustments accordingly for the 2002 marketing plan.

Costs

The budget for Agency related costs for calendar year 2001 are recommended at about $2.0MM. This will include the completion and production of the relaunch materials ($350M); ongoing new materials ($300M), Account service fee ($360M), re-development of the *Actiq*.com website ($100M), direct mail ($150M) and a journal ad program ($500M).

Pricing

High cost is one of the major reasons cited for why physicians either don't start or don't continue prescribing *Actiq*. The price of the product ranges from $7.02 to $21.05 AWP (our best estimate of the price paid by self-pay patients). This is a significant premium over competition, as generic morphine can cost as little as 50 cents or less per dose. Managed Care coverage of on-label usage is quite strong; however, it should be noted that many of our patients are Medicare beneficiaries, and may not have effective coverage of outpatient medications.

There are many factors that have affected *Actiq* price, among them the FDA's requirement that there be a significant spread between the low and high strength units to reduce the financial incentives to re-use units. Another was the need to satisfy the profit requirements of two manufacturers.

As we look to re-launch *Actiq*, we recommend that the pricing sensitivity research be repeated using the current claims and investigating usage in conditions other than cancer pain. We anticipate that updating the Simon-Kucher study would likely cost $75 to 100M and could be completed within 60 days of study initiation.

Packaging and Product Line Rationalization

Part of the complexity associated with writing Actiq derives from the current package size (cartons of 24's) and the broad range of dosage strengths.

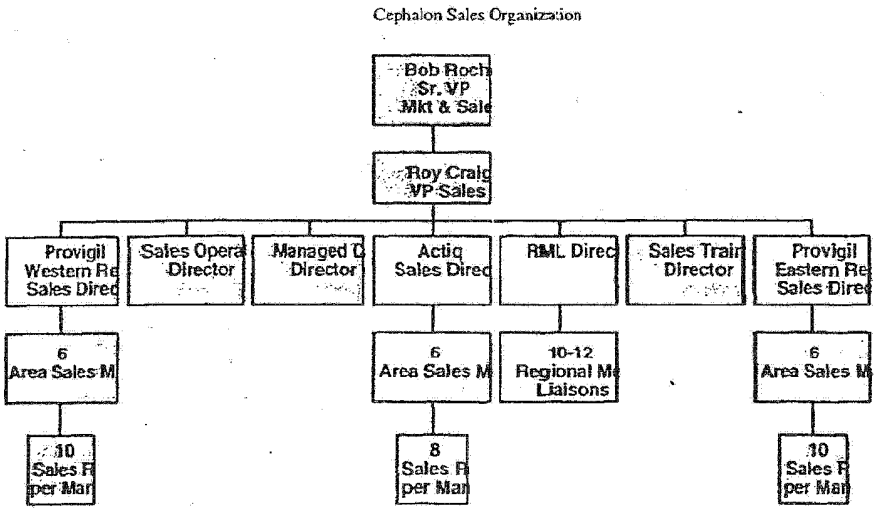
A project is currently underway to evaluate the costs and benefits of changing from the current pack size to an individual pack of 6s, four of which could then be shrink wrapped into a package of 24s. Such a configuration would be expected to help address the concerns of retail pharmacists who are unwilling to stock Actiq due to its high cost and/or who further refuse to break a carton to dispense scripts of less than 24. An analysis is also being performed to look at the distribution of the sizes of prescriptions in an attempt to determine the extent of this as a potential problem. These benefits would need to be balanced against the cost of effecting this change. A decision is planned for later this year.

We recommend that the product line be evaluated on a continuing basis to identify opportunities to reduce the complexity of the titration process by eliminating steps/strengths in the dosage offerings. We are hoping that the data from the "double barrel" PK study can be used to simplify the titration process by eliminating the requirement to trial each dosage strength.

The lower, starting strengths (200 and 400mcg), and the 800s are the strongest codes, each accounting for at least 20% of total shipments. The 1600s and 1200s have continued to increase as a proportion of total, and now represent 15% and 12% respectively. The 600s showed strength early, but is now on a steady decline as a proportion of total and now represents just 10% of unit volume.

3.2.2 Enhance Field Presence to Expand Reach and Improve Frequency and Quality of Contact

Based on discussions between Cephalon and Anesta staff, the following chart outlines the organizational structure that is in the process of being implemented for the 2001 Cephalon field organization. An *Actiq* sales director and an RML director will be added to Roy Craig's staff.



A detailed plan is in place for the development of the new field sales organization supporting *Actiq*. This organization consists of Regional Medical Liaisons who will eventually support all Cephalon products and a dedicated traditional sales organization. We envision a national sales director, plus 10 to 12 Regional Medical Liaisons in the former, and a national director, six area sales managers, plus 48 reps in the latter. We have recommended that one manager and about 20 field representatives be carried over from the Innovex organization. These people are in the process of being evaluated by representatives of Cephalon field sales management and human resources.

RML roles

While the specifics are yet to be ironed out, we recommend the following plan for the development of the RML position over the next year.

During the transition to the Cephalon *Actiq* sales organization, the RMLs will remain highly focused on maintaining the *Actiq* business and relationships, and assisting in the training and successful placement of the new Cephalon sales representatives.

At some point during the first half of 2001, the RMLs are expected to be able to take on *Provigil* and *Gabitril* activities that would be executed within the current *Actiq* called on customer groups.

From mid-2001 to mid-2002, RMLs would be expected to broaden their activities with *Provigil* and *Gabitril* in a broader set of the relevant customer groups and therapeutic areas. Specifically in the fatigue therapeutic area, RMLs will concentrate on opioid induced fatigue in cancer patients first, moving to the more general cancer fatigue marketplace (non-opioid induced), the non-cancer fatigue market (opioid induced or not), and the sleep disorder market over time (specific timeframes TBD). Of note, expansion of RML effort to *Gabitril* in epilepsy is not currently being considered.

Convention and Meeting Activity

National -- We have had limited presence at national oncology and pain meetings over the past several years. Abbott typically displayed at a small number of meetings that made sense from a corporate perspective, but placed minimal resources against *Actiq*. With only 25 people in the field and our inability to follow up, combined with our issues surrounding retention once awareness had been gained,) this activity did not seem like a good spend of time for our field resources. At this point we do not have any convention properties.

Given the increased field resources dedicated to *Actiq*, our recommendation is to plan and execute a convention program appropriate to *Actiq* that provides a significant presence at major meetings. The objective is to reach target physicians and other health care professionals outside of their office setting in a cost effective manner. To this end, we recommend designing a dedicated 10'x10' booth and attending the following meetings at a minimum:

- AAPM (American Academy of Pain Medicine) 2/14-18/01
- APS (American Pain Society) 4/19-22/01
- ONS (Oncology Nursing Society) 5/17-20/01
- ASCO (American Society of Clinical Oncology 5/12-15/01
- ASA (American Society of Anesthesiology) 10/13-17/01

In addition meetings for radiation oncologists, palliative care clinicians, and pharmacists warrant consideration.

Time is short, as new materials need to be developed. It should be noted that DDMAC has been particularly restrictive in their review of convention visuals in the past.

The anticipated budget is anticipated to be about $200M for a booth, translight production, meeting materials and attendance fees.

Note that we would recommend significant program activity at each major meeting. Dinner/lunch symposia at AAPM, APS, and ONS would run about $150M each, while a predominately social gathering at ASCO (due to ASCO restrictions on concurrent activities) would run about $50M, for a total of $500M.

Regional and Local – In the past, RMLs have coordinated speakers and display space with the sales representatives. These events have been conducted to date without tabletop displays and panel artwork.

We recommend development of 3 table top display units per district (20 total) be shared among the members of each district. The estimated cost for these display units and the accompanying artwork is estimated at approximately $40,000.

Non Personal Promotional Efforts

In addition, non-personal selling tactics are recommended to augment the efforts of the sales force to achieve the highest levels of awareness possible during the relaunch period. These include journal advertising, direct mail, and website development, all used to carry through and enhance and reinforce *Actiq* branding and core message delivery. Funding for these activities are included in the agency section above.

One area for additional consideration is an integrated direct to consumer promotional program. During late 1999 and early 2000 work was initiated to develop unbranded, breakthrough pain specific DTC advertising and a third party website hosted by ACOR (Association of On-line resources). The website is currently operational (cancer-pain.org) with a link to *Actiq*.com, while the DTC advertising effort was suspended due to concerns about lack of a critical mass of prescribing physicians and weak retail availability that would not support such an effort. When combined with the potential for a broadscale Public Relations effort utilizing the publication of the survey of 1000 cancer patients about their pain, this program has the potential to generate increased awareness of breakthrough pain and *Actiq*. We recommend $400M for a broadscale public relations program in 2001. An additional $60M may be required for ACOR maintenance.

3.2.3 Address Logistical Issues via an Integrated, Single Point of Contact and a Focused Effort to Improve Wholesale and Retail Availability

CVS ProCare (Mail Order and Limited Retail Availability)

CVS ProCare is a specialty pharmacy that offers services through a mail order location in Ohio and a retail chain of 54 apothecaries across the country. *Actiq* has partnered with CVS ProCare to allow physicians to obtain 48-hour delivery to patients at their homes via the mail order program, or to know that the apothecary network will reliably have the product in stock locally. The mail order program bypasses retail completely, which can be an important advantage in rural areas and when the patient has traveled some distance to a referral center. It can also be of significant value if the script is large or if a dosage change during the titration period would require a trip back to the physician's office to obtain the prescription.

The program was launched in August. The mail order component has been used on a limited basis, and all feedback on service levels and convenience has been very positive. It has always been positioned as a back up to retail availability in the local community, which is generally preferred by both physicians and patients. Usage of the local apothecaries is also limited. Some locations that are convenient to key physicians' offices are used quite frequently, although the apothecaries tend not to be as convenient as local pharmacies and therefore are used on an "as needed" exception basis.

Total budget for 2000 is $50M (of which $25m is set up costs, and $25M is on-going expense).

Reimbursement Hotline (Insurance coverage)

When launching *Actiq*, a decision was made to attempt to launch it "under the radar" of managed care, and not to aggressively promote or discount the product. The reimbursement assistance program was designed to assist offices and patients in obtaining insurance coverage for *Actiq*.

This program is run by Cardinal Health Reimbursement Services (aka: CRC), which provides an incoming 800 number that is staffed by dedicated, knowledgeable insurance experts who help obtain the best *Actiq* coverage for patients on a case by case basis. New call activity is holding steady, with the case load total for September at 86 hours of effort, representing 180 patients. Of note, *Actiq* is covered for most cancer patients with outpatient medication coverage, although prior authorization may be required. Many patients have run into difficulty in obtaining coverage for nonmalignant pain.

Standard reporting includes monthly activity reports plus a semi-annual report of national programs at the state level. Going forward, we recommend contracting for a state by state monthly update on all insurance plans that have been contacted. . The budget for the CRC service in 2001 is recommended at $125,000.

A complete evaluation of *Actiq*'s treatment by Managed Care Organizations should be undertaken. While in general this is not an issue for cancer pain patients, there do appear to be increasing reports of difficulty and prior authorization requirements are widespread. Once these issues can be better identified and quantified, a plan of action can be developed for the future. This plan may involve promoting *Actiq* to managed care organizations to increase their familiarity with *Actiq* and its appropriate place in opioid treatment. This could include initiating call activity on the key P & T members at target MCOs to discuss *Actiq*'s unique indication, the features and benefits of the product along with data on how appropriate treatment with *Actiq* can reduce or eliminate uncontrolled admissions and ER visits.

Indigent Patient Assistance Program

CRC also manages eligibility and intake into our Indigent program. This program is only open to patients with a cancer, although we are often asked to approve non-cancer patients.

We have served approximately 30 patients in the assistance program since its inception. In any month we have about 15-20 active patients. Of these, three patients were grandfathered into the program following the phase III studies (commitments were made to provide these patients with medication for as long as they needed it. In these circumstances, these three patients did not have effective insurance coverage). Staff time for the indigent program has declined as a result of shifting the monthly refills over to ProCare. In September just 7 hours were spent handling 38 calls for patient assistance.

On October 2, 2000 we began using the mail-order services of CVS ProCare to ship *Actiq* to patients enrolled in the indigent program. Drug is provided to these patients at cost of goods to us and will save us a substantial amount of money over the year. The anticipated budgeted for fulfillment of the indigent program in 2001 is set at $100,000. We are assuming a 3 fold increase in patient enrollment in the indigent program as we increase awareness and usage with Oncologists.

PCS Performance Script Program

The coupon program has been a very effective means for the representatives to generate trials of *Actiq*. Physicians are given a book of 5 coupon cards which when accompanied by a prescription for 6 units are redeemable for any strength at virtually any pharmacy. This allows patients and physicians to gain experience-using *Actiq* and to titrate to an effective dose at no cost, and is seen as a critically important tool by the field organization.

Over the past four months, weekly usage has averaged 87 coupons. This represents between 12 and 20% of scripts each week (depending on whether IMS or NDC data is used). To date approximately 2600 coupons have been used. Bi-weekly reports

providing excellent detail on doctors, pharmacies, patient demographics, etc. are provided to the field for use in follow up.

It is our strong recommendation that this program be extended in 2001. The total budget associated with printing 12,000 booklets (60,000 coupons), redemption (assuming 10% redeemed—a very high level), and administration is budgeted at $300,000.

Integrated Logistics Program Development

As noted above in the Agency section, *Actiq* Answers has been developed to integrate these logistics programs and increase convenience.

A variety of perceived and real barriers exist that restrict product access, prescribing, and adoption of *Actiq*. *Actiq* Answers is a comprehensive support program that has been developed to remove these barriers.

Actiq Answers is accessed via a single toll-free telephone number that health care professionals can use to:

- Obtain clinical information (Med Affairs)
- Order a patient welcome kit (Acxiom)
- Access the CVS ProCare mail order program (CVS ProCare)
- Receive patient specific reimbursement assistance (CRC hotline)
- Request a visit from a pain specialist
- Report an adverse event or product experience (Drug Safety)

The *Actiq* Answers support materials include a detail aid and a Rolodex card and magnet for the physician's office. These materials will be submitted to DDMAC by early November, with a mid-December launch. The anticipated budget for these materials is $75,000 (and is included in the agency spending section above).

3.2.4 Utilize Peer to Peer Influence Opportunities to Generate Product Interest and Overcome Prescribing Objections

Teletopics

Teletopics is designed to provide third party medical education about Breakthrough Pain and *Actiq*. This is a cost-effective program that reaches a large and geographically diverse target audience in a timely manner. The teleconference format allows for better-cost and time efficiencies in comparison with traditional peer to peer selling events.

This program features Ann Berger, Chief of Palliative Care at the National Institutes of Health. A 25-minute video is played at each site, and then the attendees participate in a live interactive Q & A session hosted by Dr. Berger. This is often the most valuable part of the program, as it tends to focus in on the "how tos" of writing *Actiq*.

During a five month period, we have completed 19 of 23 scheduled programs with over 200 individual sites and over 1,950 attendees (MD's, RN's, RPh's).

In the very tough to penetrate Oncology offices, we've found that Teletopics has given reps an opportunity to gain valuable face time and build rapport with office staff and physicians. We have received numerous reports of prescriptions being generated by these programs although limitations on our ability to track participation has hampered completion of a quantitative ROI analysis. That said, we believe that this program is a very economical way to reach a widespread audience, quickly and efficiently, while enhancing rep access to hard to reach offices.

Our strong recommendation is that this program be continued in 2001 with at least one new program featuring a new presenter. The recommended budget is $250M for 20 programs over a 4 month period for the development and execution of a new program and $100M for the continuation of the existing Berger program over 35 new dates. Total budget is $350M.

Speaker Fly-Away Meetings

In February of this year we held a speaker training session in Phoenix, AZ and in May we hosted a second similar program in Tampa, FL. These programs were designed to provide an opportunity for in-depth presentation, education and discussion about BTCP and *Actiq* to provide new insights for peer-to-peer education.

For each meeting we selected a faculty of 4-5 pain and oncology clinicians who were avid *Actiq* prescribers to present clinical data and case reports using *Actiq*. The RMLs have played an active role in these sessions, developing stronger relationships with these champions.

In addition to creating *Actiq* speakers, these programs generate immediate script impact.

The actual productivity of these meetings needs to be more directly assessed before a decision can be made on recommending their continuation in 2001. While they appear to be very effective in increasing physician activity, we have recently become aware that much of the growth is attributable to a very small number of physicians.

We believe these meetings generate a tremendous amount of goodwill and have been a significant factor in the success of *Actiq* to date. Assuming the financial analysis support it, we would recommend these programs be run on a semester basis, at a cost of about $275M per meeting, or $550M for the year.

To date, nothing has been initiated for 1Q2001. We feel that there are a significant number of potential attendees given the time that has lapsed since our last meeting in May and the strong increase in the number of new writers as shown by the Xponent cohort analysis, and recommend that initial planning begin immediately.

3.3 Medical Affairs

The transition of Medical Affairs for OTFC products is well underway. A meeting was held in Salt Lake City in mid-October between individuals from Medical Affairs at both sites. Plans were outlined to make the transition of activities to the West Chester office. A follow-up-meeting is scheduled of the end of October that will include in an in-depth review of the *Actiq* data and related issues.

What follows is a description of how these functions have been handled at Anesta, and what transition steps have been taken to date.

Information Requests have been handled by Anesta Medical Affairs with assistance form individuals in Drug Safety. Phone calls are triaged by drug safety and follow-up letters and reprints, when appropriate, are sent out by Medical Communications. Fax, e-mail, letter, and Internet information requests are handled directly by Medical Communications.

- Electronic copies of standard and custom information request letters have been transferred to West Chester
- Current 1-880 SLC numbers have been provided to West Chester to factor into a new combined phone system.
- A database of OTFC related information requests will be kept in SLC until the time of transfer of the process to West Chester. At the time of transfer further requests will be entered into the West Chester database. The SLC database will be kept separately without attempting to merge the data into the West Chester database.
- A report of OTFC related database of abstracts, manuscripts and other printed materials has been transferred to West Chester.
- Training has been scheduled for the SOS group in Atlanta for late November.

Publication Planning at Anesta was a joint effort of Medical Affairs, Marketing, and Clinical Drug Development. Medical Affairs has managed the process.

- The medical writing group in West Chester has been provided with the *Actiq* publication plan.
- Weekly update phone calls have begun. Julie Jenkins is the contact person in SLC

Sales Training on the medical aspects of *Actiq* has been handled primarily by Steve Shoemaker. A series of four *Actiq* training modules have been used for home study prior to classroom training. New sales representative are given a "certification test" to ensure that they understand the *Actiq* PI and the Risk Management Program.

- *Actiq* sales training modules have been sent to West Chester
- The participant guide to the training modules has also been transferred.
- Electronic copies of the sales training files have been transferred.

- Sales training with support from Steve Shoemaker has been scheduled for early December.
- An electronic version of the frequently asked questions was transferred along with "broadcast" e-mails sent out to the sales force.
- Electronic copies of certification tests and answer keys will be transferred

Medical Education meetings designed to update clinicians on the practical issues of *Actiq* use have been coordinated by Marketing and Medical Affairs. A key objective of these meetings has been to stimulate a dialogue between high prescribers of *Actiq* and occasional prescribers to address logistical issues related to prescribing the product.

- Current *Actiq* thought leaders were reviewed in detail
- Hard copies and electronic version of slide module have been transferred

European Partner Training has been handled by Medical Affairs with a marked increase in activity in 2000. This has included a basic introduction to the clinical pharmacology and clinical trial program for *Actiq*, and more recently a "Train the Trainer" session to introduce the partners to the specifics of our current sale training program.

- The most pressing need at this time is training of the Elan sales force for launch of *Actiq* in early 2001. The timing and potential Medical Affairs involvement in this training has not yet been defined.

Graphics Support has been provided throughout the company by Anesta Medical Affairs. This has included the production of poster presentations for scientific and medical meetings, slide kit production, instructional brochures, patient education materials, and Internet and Intranet support.

- Electronic files from the SLC MedComm server will be transferred to West Chester by a process being coordinated by the IT departments at both sites.

4.0 Clinical and Regulatory

4.1 FDA "Level Playing Field" Strategy

From its initial submission, through the approval process, and in the post marketing period, *Actiq* has been scrutinized especially closely by FDA. The impact is felt most acutely when comparing *Actiq* claims versus those that our competitors are allowed to make. This comparison leads us to believe that *Actiq* is currently competing on an "unlevel" playing field, and that a complete examination of our regulatory strategy should be undertaken.

Working Group

We recommend that a multi-functional working group be convened to develop a Regulatory strategy for *Actiq*. Representatives of Clinical, Legal, Marketing, Medical Affairs, and Regulatory, together with outside consultants and counsel should be included. This group should include people with experience with the product history to provide context as well as "new blood" to provide fresh perspectives.

Issues for consideration by this group are outlined below. Others should undoubtedly be included:

- *Actiq*'s very narrow indication. This is the first time that an analgesic has ever been so tightly restricted in terms of a very specific type of pain (breakthrough cancer pain) in a very specific patient population (opioid tolerant patients with malignancies). More commonly, clinical data from one pain model is allowed to be applied to anlagesia in general. By the Agency's own admission, these restrictions were established for social considerations and were not derived from any clinical experience.

- Washington Legal Foundation (WLF) – Abbott had taken a very conservative approach to usage of journal articles under WLF. We conducted our own examination of our options in this area and unfortunately were not able to identify acceptable options given the newness of this avenue. This needs to be revisited as the limits of WLF become better defined.

- Competitive claims – FDA has shown an unwillingness to respond to our complaints about promotional activities by our competitors. We have provided three letters to FDA starting in March of 1999 relating to: 1) promotion of other products for the indication of breakthrough pain, despite a lack of clinical support for efficacy in the condition 2) positioning of competitive products as providing "rapid" action either based on no data or on blood level data. These arguments are quite strong and the letters (which were drafted by FDA ex-General Counsel Tom Scarlett and therefore are referred to as the "Scarlett Letters").

  A companion argument to the FDA's unwillingness to address these concerns is the

extremely tight control they have exercised over the *Actiq* promotional claims via their review process. Specific areas for consideration will be further identified in a meeting to be held on November 7.

- Exclusion of FDA-required studies from the label – FDA agreed to a clinical program containing six key studies. During the label negotiation process, any mention of two of the six were stricken from the label by FDA, even though we believe that they contain information highly relevant to prescribing this novel product. The excluded studies were the AC600-010 study (comparison to IV morphine in post-operative pain) and AC600-015 (use of OTFC as the sole opioid to treat cancer pain).

- Subpart H – *Actiq* was approved under Subpart H, regulations that provide FDA with the authority to require compliance the *Actiq* Risk Management Plan and effectively provide much greater control over promotional activities. Of all the RMP provisions, it is probably the 30 day advance review of materials that is most onerous for *Actiq*. We understand that at least one other products approved under subpart H have been successful in obtaining 24 hour turn around on materials.

  While onerous, there are portions of the RMP that may provide some protection from generic competitors, and the impact of the program needs to be carefully evaluated in this context before any recommendations about potential changes are made.

- *Actiq* claims – While these will be better defined at a series of upcoming meetings, one area of particular interest is the future use of the AC600-001 trial which compared *Actiq* to oral morphine in a double blind, double dummy comparative trial. Patient preference claims are also of special interest, based on research with physicians that clearly indicate this as being among the most powerful statements that could be made on behalf of a product.

4.2 SNDA Clinical Target Labeling

During the negotiation of the final label with FDA in November 1998, it became apparent that we were going to want to make changes to the *Actiq* label as clinical data became available to support those changes. Our experience marketing the product over the past 18 months has confirmed these needs and helped us refine the information to be added. What follows is a very brief summary of the changes currently planned, followed by more in-depth description of the current working draft verbiage.

1. Onset of Action (AC600/007) –adds pharmacodynamic information from our pupillometry study to provide comparative onset of effect versus MSIR to the pharmacology section. The underlying principle is that miosis can be used as a surrogate marker for opioid effect.

2. Estimation of the potency ratio to morphine (AC600/007, AC200/017) – provides pharmacodynamic information that will increase our understanding of relative potency based on the pupillometry study and our study comparing respiratory depression between *Actiq* and morphine

3. Simultaneous dosage study (AC600/005) – provides pharmacokinetic information on simultaneous consumption of two 400mcg units compared to one 800mcg unit. Our hope is to be able to answer this very frequently asked question (do two units of one strength equal a double strength unit). A successful outcome here should allow us to simplify the titration process.

4. Comparative study versus MSIR (AC600/001) – provides superior efficacy information in this head to head, double blind comparison of *Actiq* and MSIR both from an efficacy perspective, and also in terms of patient preference. The latter may actually be of more value from a marketing perspective. Note that this is a single study, and typically two studies are required for a superiority claim. Determining how to approach FDA with this information needs to be considered as part of our overall regulatory strategy.

5. Update on safety experience – Without redoing all of the safety tables in the PI, we are interested in adding a statement incorporating the 187 MSIR and UK trial patients to the total patient base (currently 257).

4.3 Phase IV Plans

In this discussion the term "Phase IV" covers studies carried out on a marketed product, whether or not these studies are carried out under an IND.

Phase IV plans for the 1999 and 2000 calendar years were developed by Clinical Development in consultation with Marketing and Medical Communications. Phase IV planning to date has been confined to the United States.

Active Projects

The year 2000 Phase IV program is summarized in the attached table. The 18 studies listed in the summary table are active and either in IRB review/start up, in-life or reporting status with the following exceptions:

- AC 600/003, a Phase IV commitment study in pediatrics is on hold at FDA request pending FDA division and pediatric advisory committee input on design. Anesta had previously submitted a synopsis of a proposed protocol and had discussion with the reviewing division.
- AC600/010, a pharmacokinetics study in-patients with mucositis, has been delayed due to inadequate accrual on the pilot study AC600/008. In view of the experience of AC600/008 the viability of this study needs to be reconsidered.
- AC600/011 is in the design phase at this time with a target of 1Q 2001 for start up.

Preliminary Phase IV Plan for 2001

The Preliminary Phase IV plan for 2001 will

1. complete the AC600/004 pilot study of *Actiq* as a sole analgesic for use on a prn basis
2. complete and report AC600/009 (*Actiq* vs. MSIR comparative trial)
3. complete and report AC600/010 (mucositis PK), pending a decision to go forward
4. carry out the in-life portion of the AC600/011 (comparative pupillometry vs. oxycodone, hydrocodone, hydromorphone)
5. implement AC600/003 (pediatric study) if FDA requires it and agreement can be reached on design issues.

Investigator-initiated trials

We had commissioned a review group consisting of Clinical, Medical Affairs, Regulatory and Marketing representatives to review and make determinations of support for incoming investigator initiated studies, and recommend that *Actiq* be included in the Cephalon system going forward.

All additional clinical trials effort will be directed toward indication expansion in acute pain and in non-cancer breakthrough pain which are discussed separately in section xxxx.

Summary of OTFC Clinical Trials

Protocol	Description	Status	Purpose	Next Steps
AC 200/014	An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (*OTFC*) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other *OTFC* Studies	Treatment Completed 164 patients Unreported	To establish the long-term safety and tolerance of OTFC in cancer patients experiencing breakthrough or incident pain while taking other opioids.	Complete final report; submit to FDA and have available for MAA as needed. Publish?
AC 200/016	A Double-Blind, Randomized, Parallel-Group Study Comparing Oral Transmucosal Fentanyl Citrate (*OTFC*) to Intravenous (IV) Morphine and the Related Effects of Respiratory Depression	Treatment Completed 30 subjects Unreported	To establish the dose equivalency (relative potency) of 3 doses (3,6 or 12 mg) of IV morphine and 3 doses (200, 400, or 800 mcg) of *OTFC* using resp. depression as endpoint, and to define the time course of resp. depression with both *OTFC* and IV morphine.	Complete abbreviated final report and submit to FDA.
AC 200/017	A Double Blind, Randomized, Double-dummy, Crossover Study Comparing Oral Transmucosal Fentanyl Citrate (*OTFC*) to Intravenous Morphine Sulfate (IVMS) by Evaluating Dose-related Respiratory Pharmacology	Treatment Completed 38 subjects Unreported	To evaluate the magnitude and duration of respiratory depressant effects of *OTFC* and IVMS and to establish relative potency of the two drugs	Complete final report; submit to FDA and have available for MAA. sNDA? submit information for label change? Publish
AC	A Multicenter, Double-Blind,	Treatment	Compare *OTFC* to IR morphine	sNDA: submit

600/001	Crossover Study of Oral Transmucosal Fentanyl Citrate (*OTFC*) Compared to Immediate Release Morphine Sulfate for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Opioids	Completed 134 patients Reported Publication pending	for the treatment of breakthrough pain.	information for label change. Await publication in PAIN for use in field. Additional publications?
AC 600/002	An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (*OTFC*) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in AC 600 Series Protocols	Treatment Completed 68 patients Unreported	To establish patient preference for IRM or *OTFC*, and to establish long term safety and tolerability.	Complete final report; submit to FDA and have available for MAA. Publish?
AC 600/003	*Actiq*® in children with breakthrough cancer pain.	On Hold. Synopsis submitted to FDA and we were instructed to await their response.	Phase IV Commitment: Assess use in children.	Awaiting response from FDA as to whether this study will be required.

Summary of OTFC Clinical Trials (continued)

Protocol	Description	Status	Purpose	Next Steps
AC 600/004	An Open Label Study of the Safety and Efficacy of Oral Transmucosal Fentanyl Citrate (OTFC®) as a Sole Agent for Cancer Pain	Protocol being finalized 24 patients planned	Assess use as ATC medication using MEQ chart.	Finalize protocol, CRF, initiate site and ship study drug.
AC 600/005	An Open-Label, Randomized, Two-Period Crossover Study of The Pharmacokinetics and Safety of Fentanyl Administered to Healthy Human Volunteers as Two 200 mcg OTFC Dosage Units or as One 400 mcg OTFC Dosage Unit	Treatment Completed 12 subjects Unreported	PK: 2 x 400mcg vs 1 x 800mcg	Complete final report. sNDA: submit information for label change. Publish
AC 600/006	Evaluation of *Actiq*® Titration Practices in the Clinical Setting	Treatment Ongoing 293/≈1000	To evaluate the titration process of *Actiq* when prescribed for the management of breakthrough cancer pain.	Determine whether to continue study (meeting scheduled 27Oct00). Determine whether post-study investigator meeting is of value for gathering clinical experience information.
AC 600/007	The Time Course of Pupillary Changes following OTFC® and	Treatment Completed 47	PD: Compare time to onset of miosis (OTFC vs MSIR)	Complete final report and submit to FDA.

	MSIR® in Healthy Volunteers: A Randomized, Double-Blind, Double-Dummy, Parallel Study	Unreported		sNDA: submit information for label change. Publish
AC 600/008	The Tolerability of Oral Transmucosal Fentanyl Citrate (OTFC®) in Patients with Grade 3 or 4 Oral Mucositis: A Randomized, Double-Blind, Crossover Study	Treatment Ongoing 3/12	Evaluate whether patients with mucositis can tolerate OTFC	Determine whether to continue study (meeting scheduled at end of Nov00).
AC 600/009	The Pharmacokinetic/Pharmacodynamics of OTFC® and MSIR®: A Randomized, Double-Blind, Double-Dummy, Crossover Study	Under IRB Review	PK/PD: Compare time to onset of miosis (OTFC vs MSIR). Provides supportive data for AC 60/007.	Need CRF and stat plan. Initiate study and ship study drug.

Summary of OTFC Clinical Trials (continued)

Protocol	Description	Status	Purpose	Next Steps
AC 600/010	TBD	Planned	PK: OTFC in patients with mucositis	Determine need.
AC 600/011	TBD	Planned	Compare time to onset of miosis for: OTFC vs oxycodone, hydrocodone, hydromorphone	Finalize comparators and draft protocol.
AC 800/001	A Double-Blind Comparison of the Analgesic Efficacy of the Fentanyl Oralet and Oral Morphine in Pediatric Patients Undergoing Burn Dressing Changes and Tanking	Treatment Ongoing 1/30	Compare the efficacy of Oralet to oral morphine in the pediatric burn patient population.	Continue to monitor progress.
AC 800/002	Role of CYP3A4 in OTFC Fentanyl Disposition	Treatment Ongoing 0/24	To determine whether altered CYP3A4 activity results in altered OTFC disposition and clinical effect.	Continue to monitor progress.
AC 800/003 (Abbott 96011)	Premedication with OTFC for Reduction of Postoperative Agitation in Pediatric Ambulatory Surgery with or without Ondansetron	Treatment Completed. 125 patients	To assess whether OTFC reduces post-op agitation and whether ondansetron reduces the incidence of post-op nausea & vomiting following OTFC.	Manuscript submitted to Anesthesia & Analgesia 07Aug00.
AC 800/004 (Abbott 98006)	A Double-Blind Comparison of Fentanyl Oralet and Oral Oxycodone for Outpatient Burn Wound Care in Children	Treatment completed. 22 patients	Compare the efficacy of Oralet to oral oxycodone in the pediatric burn patient population.	Abstract being submitted to ABS (deadline is 05Oct00)

4.4 Indication Expansion

Actiq's approved indication is "...only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain." This is the narrowest indication among all opioids, as it specifies a degree of opioid tolerance and a particular disease condition. (Virtually all other opioids are simply indicated for moderate to severe pain.) Eliminating both of these limitations would be expected to significantly expand the *Actiq* opportunity. We recommend the following stepwise approach:

1. The limitation to breakthrough cancer pain seems to be the easiest, and should be attacked first. This limitation is not well-founded in the data, and we believe that changing the indication to breakthrough pain without limitation to cancer etiology should be achievable with very limited additional clinical work.

2. From there the next step would be to introduce data to expand the indication to allow usage of *Actiq* as sole opioid therapy for chronic cancer and/or nonmalignant pain, or for other uses other than breakthrough pain in opioid tolerant individuals.

3. The third step of extending use to acute pain treatment will be the most difficult and time consuming. The rewards could be huge, but so is the risk, as it may be quite difficult to identify and safe and effective dose. Of note, we currently have a black box prohibition against use in acute pain and in opioid naïve patients, and it is expected to be very difficult to get this contraindication removed.

Additional discussion and detail on each of these steps follows below.

Breakthrough Pain Indication for Non-Malignant Chronic Pain

The history of the U.S. approval of *Actiq* for use only in cancer patients with breakthrough pain reflects of a set of complex social and political considerations, rather than data associated with the product itself. The indication language in the UK allows for usage in "breakthrough pain", thereby implicitly including nonmalignant pain conditions.

With this in mind, we propose that the strategy for expansion to non-cancer breakthrough pain focus on regulatory strategy and negotiation rather than the accrual of clinical data.

We recommend approaching FDA to schedule a quasi- "end of phase 2" meeting where we can discuss the inherent inequity and illogic of this position. We would additionally argue that the experience and data in cancer BTP can and should be extrapolated to non-malignant BTP and that that the risk/benefit ratio is a least as favorable. Whether there are specific data which could be collected to address FDA's expressed concerns that non-cancer patient's do not have well-developed "support systems" that can assist in safe usage warrants investigation. In addition a

small observational clinical trial could be offered, with the very specific argument being made that one or more adequate and well controlled clinical trials should not be required for this indication expansion.

While we are hopeful that this proposal will be accepted by FDA, we also believe it is unlikely that it will. Proposing it will force the Agency to set forth what they will expect as a pathway to approval, which can then be negotiated and defined prospectively. Once defined the company can then determine whether the requirements for approval are feasible.

At the same time, we recommend creation and implementation of a plan to publish data on *Actiq* usage in nonmalignant pain. This could then be used to broaden product usage in advance of any labeling change under the Washington Legal Foundation case. It is important to note that such studies may well require an IND as they would be considered "off label" under the current indication.

Chronic Pain Indication (as sole analgesic dosed prn)

A further area of indication expansion is currently beginning pilot clinical evaluation. A pilot study of *Actiq* as substitutive therapy for a single analgesic on a prn basis in patients with cancer is currently being started up (AC600/004). The economic viability of using *Actiq* as substitutive therapy is uncertain at this time. While the clinical feasibility of this approach is also uncertain, we do have some data from the AC200-015 study that provides encouragement. In that study, patients used *Actiq* as their sole opioid therapy. Patients were individually titrated, and used doses administered 4 to 6 times daily to achieve effectiveness and safety compared to their previous opioid regimen that included around the clock and breakthrough pain medications. In addition, there was no undue drug accumulation, which had been the stated reason for conducting the study in the first place.

The following table summarizes the recommended priority and sequencing of the various chronic pain conditions:

	Cancer (opioid tolerant)	Non malignant (opioid tolerant)
Breakthrough	Currently approved	Priority #1
Other chronic	Priority #2	Concurrent with Priority #2 or as Priority #3

Acute Pain Indication

The market for acute pain treatment is very large , and assuming that this should be made a priority for further evaluation and development, we recommend the following approach.

Key assumptions

The following clinical development synopsis is based on a number of assumptions:

1. Fentanyl is a well—known and well-characterized analgesic. The analgesic activity of OTFC has been well demonstrated in breakthrough cancer pain

2. There is no reason to believe that OTFC's demonstrated activity in breakthrough cancer pain would not be translatable to the management of acute pain of moderate to severe intensity.

3. Various opioids are approved for use in the management of pain including acute pain and are recognized as safe and effective.

4. A substantial amount of clinical data on administration of the 800 mcg dose of *Actiq* in healthy, opioid tolerant volunteers exists. These data, which include studies which were part of the original NDA as well as additional studies, should be rigorously reevaluated in order to put aspects of *Actiq*'s potential for respiratory depression into perspective and to understand better the instances of respiratory depression which have been reported.

5. Data exist which allow relative potency comparisons with regard to respiratory depressant effects and analgesic effects between OTFC and intravenous morphine (and by extension to other routes of administration for morphine and to other opioids through the use of literature data).

6. Based on 5) it will be possible to estimate doses of OTFC for use in non-tolerant patients with acute pain which should have comparable analgesic effect and respiratory depressant effect to approved (and recognized as safe) doses of other opioids.

7. The doses identified in 5) can be tested in a simple clinical pharmacology study to confirm equivalence of respiratory depressant effects.

8. A subsequent study or studies in acute pain syndromes would be used to provide confirmation of safety and efficacy in patients. The emphasis here would be to try to steer FDA away from large, complex or rigorous studies on the grounds that fentanyl is well demonstrated to be an analgesic and that its respiratory pharmacology as compared to approved drugs and doses has been well characterized in 7).

9. Anything beyond a single study and any increment in sample size beyond that required to carry out hypothesis testing should be negotiated with FDA in a pre-development meeting.

Development sequence

With the above in mind the following development sequence is proposed:

1. Develop estimate of OTFC doses with equivalent respiratory depressant effect and equal or greater analgesic effect to oral morphine sulfate, oxycodone and hydromorphone from existing data (AC200/010,and 017, AC600/007).

2. Confirm estimates in a study in healthy volunteers and complete data analysis. (The study envisioned would be very simple. Administration of the study drugs in a double blind crossover design with placebo control arm as well. Subjects are monitored via SPO2 and respiratory rate (and perhaps some indirect measurement of tidal volume) in a minimally stimulated environment. The sensitivity of this model might be increased further by carrying out this study in a sleep lab environment.

3. Meet with FDA and present data demonstrating that one or more dosage strengths of OTFC are equivalent in respiratory depression and greater than or equal in analgesic effect to one or more of the approved products which have been approved for and safely used in opioid non-tolerant individuals. Also present in detail data in non-tolerant volunteers at 800 mcg (which should be substantially higher than the intended doses in acute pain) to put safety into perspective.

4. Negotiate a pathway to approval in acute pain based on a study or studies providing a simple confirmation of efficacy and confirmatory evidence of safety in an outpatient in one or more acute pain settings (e.g. fractures, arthroscopic surgery, trauma, etc.). Whether or not to consider offering FDA a study in a hospitalized population as either a precursor to outpatient studies or in support of a hospital only indication needs to be debated. In order to provide some perspective for any observations of possible respiratory events, an opioid comparator should be included in any study which is done and the collection of data related to potential respiratory events should be carefully structured and prospectively defined.

Note: The above assumes that agreement with FDA will be attainable and that development would then proceed in the US and EU in parallel. If agreement on a development plan cannot be reached with FDA the organization will need to decide if exclusively ex-US development should be undertaken.

4.5 Runway Extension

The goal of the "runway extension" project is to implement strategies leading to the effective extension of the patent life of *Actiq*® and develop ancillary strategies for slowing the introduction of competitive products. The project has involved four types of activities:

1. Monitoring and surveillance of potential non-OTFC competition
2. Patent and trademarking strategies
3. Regulatory nomenclature
4. Anti-ANDA activity

Monitoring and surveillance of potential non-OTFC competition

The Office of Development has developed and maintains a searchable database of companies with products and development projects in the fields of alternative drug delivery and pain/palliative care. The database is used to enhance our knowledge and awareness of potential competitors, to identify potential acquisition candidates, and to provide creative input to our product development programs. Cory Pike, Cephalon SLC's librarian, maintains the database and can assist people with searches.

Patents and Trademarks

The goal of patent activities in this area is to file new cases, with a new 20 year term, designed to protect *Actiq* from generic competition beyond the expiration date of our core U.S. patents in 2005. Two of these patents describe new learning in the use of *Actiq* to treat breakthrough pain and the art around the specialized manufacture of our unique *OTS* dosage form. Specifically:

- We are finalizing a draft entitled "Compositions and methods of manufacture for oral dissolvable dosage forms". The patent describes handless lozenge versions of *Actiq* and is designed to block the development of a lozenge competitor product. This patent will be filed under a Request to Make Special in order to more quickly determine if it can be filed as a new, independent case.

- A patent entitled "Method and apparatus for treating breakthrough pain" is in advanced draft form and under review by the authors (Steve Shoemaker and Dennis Coleman). This patent describes methods and formulations for treating a patient's breakthrough pain by matching a pharmacokinetic profile of analgesic serum concentration that mirrors a patient's breakthrough pain profile.

- A manufacturing patent that describes the manufacture of pharmaceutical dosage forms with handles has been outlined. This patent will claim the many techniques that we have developed which are unique to the manufacturing of pharmaceutical dosage forms with

handles. We believe that this patent will offer significant protection for *Actiq*, as well as our other products that utilize the *OTS* delivery system.

- The *Actiq* trademark is registered in the United States and 12 other countries and is pending or approved for registration in another 11 countries. In addition, Anesta has filed a trademark application in the United States for the appearance of the unit in order to protect the product's appearance

Regulatory Nomenclature

The goal of this aspect of the project was to tie the terminology used to describe our products in regulatory documents to our patents. We believe that an official FDA product description that includes the presence of the handle can serve to protect us from a competitive fentanyl lozenge ANDA. To this end, we requested that the FDA change the description of our product in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (aka "The Orange Book"). The current Orange Book description of our product dosage form is "troche/lozenge". We requested that it be changed to "lozenge, with handle". Unfortunately, the FDA denied our request. However, the UK Regulatory authorities describe our dosage form as "lozenge with integral oromucosal applicator" (not quite the terminology we requested but it does include the handle designation).

In the future, Cephalon may want to consider submission of a monograph to the USP regarding manufacturing of *Actiq*. Fentanyl itself is already compendial under USP. Anesta's Quality group has the necessary SOPs that can be reformatted to USP requirements in order to accomplish this. A risk/benefit assessment of this strategy will need to be conducted since the monograph might contain trade secret information regarding our manufacturing processes that could offset the benefits of making the product compendial under USP.

Anti-ANDA Activity

The goal of this aspect of the project is to use the Risk Management Program (RMP) as a barrier to entry for generic competition. The RMP is a program of safety measures that the FDA imposed as a condition of *Actiq* regulatory approval. One of these safety measures is that Anesta must make available a child resistant interim storage device for partially consumed *Actiq* units. We have recently received a Notice of Allowance for our patent entitled "Methods and Apparatus for the Interim Storage of Medicated Oral Dosage Forms" which describes the use of a child proof storage device that parallels the requirements of the RMP. Since a generic version of *Actiq* would presumably need to assume the same RMP, we believe that this patent will make it more difficult for a generic to effectively meet the requirements of the RMP without violating our patent.

Future activities include maintenance and expansion of the current patent portfolio around *Actiq*, its therapeutic applications, and its manufacturing processes. Kim Rogers (SLC) will be working

with Bob Hrubiec (WC) to transition and coordinate the intellectual property management between SLC and West Chester.

5.0 Manufacturing/Operations

5.1 Transition from Abbott to SLC Manufacturing

Current Situation

Actiq®is manufactured in Abbott's N. Chicago Hospital Products Division, physically located in their Large Volume Parental (LVP) Business Unit. The formulation is a cooked-sugar or cooked candy process, originally developed for Fentanyl Oralet® in the early 1990's. It is a custom process, using specialized equipment. A new compressed powder formulation was developed in SLC and has been approved for manufacture into the UK market.

Since the increase in sales of *Actiq*® following re-acquisition of the product from Abbott, the LVP operations group has struggled to manufacture and release product to maintain a target of 10 weeks of inventory.

The drivers for the transition to SLC manufacturing are, as follows:

24. Improved reliability of supply
25. Major cost savings (in the neighborhood of 50 cents per unit)
26. More "FDA-friendly", pharmaceutically elegant dosage
27. Internal control for long-term protection

The timing for this change is critical, based on our supply agreement with Abbott. We are committed to informing Abbott on October 1, 2001 of our intentions to 1) transfer manufacturing to Salt Lake City by March 31, 2002 or 2) have Abbott continue to make the product for up to twelve months. We have to be prepared for the review and approval of the sNDA to take up to 12 months due to its complexity (despite the "official" review time for the sNDA of 4-6 months).

Short Term Projects

Preparation of a Supplemental NDA.

Preparation of a supplemental NDA (sNDA) to provide for change in formulation/packaging and the site change from Abbott N. Chicago to Cephalon SLC Division. For the CMC section update this will require a cooperative team effort across Regulatory Affairs, Manufacturing and QC Operations, QA and R&D. The target for approval of the sNDA is the end of 3rd Quarter 2001.

Ken White is now handling regulatory contact for this project.

The initial step was an IND amendment, submitted October 12th. This highlighted the stability protocols used to support the 24-month dating approved by the UK, consistent with ICH guidelines. It also presented the new compressed powder dosage form and blister packaging and the rationale for bioequivalence.

The critical path for the submission is to request a pre-submission meeting with FDA to discuss several topics that could be controversial in this submission, including the following:

- Changes to the product appearance and packaging (a new handle, for example, given the current product definition in the Risk Management Plan), as well as issues related to changes in the packaging materials.

- Stability protocol. Accelerated and long-term stability tests are being conducted in accordance with ICH guidelines to determine the effectiveness of the barrier properties of the unit dose blister pack. A proposed stability protocol was submitted to FDA for their review and comment (see IND 27,428, Serial No. 426).

The next step is to schedule a meeting with FDA to discuss the acceptability of the new handle/tag and blister package, consistent with the RMP. Confirmation of the stability protocol and bioequivalence package should be obtained. Initial feedback from FDA suggests that they are not eager to grant the meeting request.

Following this definitional meeting, we would be able to assemble the CMC section for the supplement to support the FDA SUPAC filing requirements. This filing involves five major SUPAC changes, requiring pre-approval by FDA, in a six-month review process :

- Active Pharmaceutical Ingredient (API) change, including both spec and supplier source
- Major formulation change
- Manufacturing site change
- Container/closure system change (a modified EU blister pack),
- Test methods and specifications changes

In parallel, we need to initiate a PK study to support the product performance on the high end of the release pH range (@ 6.5). Carl Roland and Paul Litka will present the need for this study in West Chester.

The two major objectives are: 1.) to provide data to support a wider specification at the upper end of the pH range (i.e. greater than pH 6.5); and 2.) to provide PK and safety data in the event a sample from a commercial lot exceeds the upper limit of pH 6.5. Hopefully, these data would help QA avoid a recall situation This is not a bioequivalence study and will likely involve using 6.5 as one of the test points, with something like 6.3±0.2, 6.6±0.2, 6.8±0.2 and 7.0±0.2.

Label copy changes

A plan is in the process of being developed to replace Abbott artwork with Cephalon artwork, including new NDC numbers.

Six pack carton

A project is underway to implement a six-pack carton to replace the twenty-four counts carton, while the product is being manufactured in N. Chicago. Third party packaging at PCI is also under consideration. It may be faster, but will be more costly than using an in-line modification at Abbott.

Longer Term Projects

- Pass FDA site GMP & PAI inspection at the SLC Manufacturing facility. This will be scheduled in conjunction with the sNDA filing.

- Transition inventory from Abbott N. Chicago to Cephalon SLC manufacturing following sNDA approval. The targeted timeframe is between 3rd Quarter 2001 and 1st Quarter 2002, in accordance with the Abbott supply agreement.

- Execute Facilities investment to support 3 to 5 year Euro and US unit volumes. Comprehensive architectural & engineering analysis of the SLC facility to meet both EU and US *Actiq* manufacturing needs is underway and is anticipated to be completed by year-end 2000. The integrated project services firm, IPS, with significant pharmaceutical experience, has been employed to develop manufacturing options for the five-year manufacturing strategy. This work will be coordinated with the full supply chain plan.

- Possible implementation of an improved CR packaging, which would be scissors-optional, as opposed to scissors-required.

5.2 DEA and Vault Storage Considerations

Current Situation

Actiq® contains fentanyl, a controlled substance subject to both U.S. and international regulatory restrictions.

Storage restrictions in the U.S. require a DEA approved vault with restricted and controlled access. Additionally, the DEA prohibits re-exportation of schedule II product exported from the U.S. Member states of the EU do not share the DEA's view on re-exportation, especially within the EU countries.

Two issues pertaining to DEA restrictions currently impact our ability to meet projected manufacturing growth for the EU and the U.S. of the compressed form of *Actiq*. The first issue is the small size of the vault in the SLC facility. The second issue pertains to the DEA restriction of re-exportation of *Actiq*, which prevents us from setting up a package labeling and/or distribution center in one EU member state for the purpose of supplying other EU member states. These re-exportation restrictions also prevent us from considering cost cutting measures such as assembling and packaging *Actiq* in one EU country for the purpose of supplying other European countries.

Short Term Projects

Vault expansion for EU manufacturing and initial US transition volume

The west-end *of* the SLC facility will be remodeled to include an expanded vault that would utilize the previously sub-leased space to provide for Euro manufacturing and provide some short-term options for *Actiq* growth and US transition to SLC manufacturing.

The preliminary cost estimate for the west-wing vault is roughly $750,000. This expenditure will provide roughly 400 pallet spaces by using high-efficiency racking in the low ceiling facility constraint. More detailed estimates are dependent on DEA allowance of alternate construction approaches. Vault plans will be available for review and finalization in November.

Construction is targeted to begin by December, 2000, with completion scheduled for 1st Quarter 2001. This is contingent upon DEA acceptance of our design parameters.

Longer Term Projects

Comprehensive architectural & engineering analysis of the SLC facility to meet both EU and US *Actiq* manufacturing needs is underway.

This project is anticipated for completion by year-end 2000. The integrated project services firm IPS has significant pharmaceutical experience and has been employed to develop manufacturing options for the five-year manufacturing strategy. This work will include consideration of any further vault expansion required for full US *Actiq* volumes. This work will be coordinated with the full supply chain plan, including vault capabilities at DDN/Obergfel to store finished product requirements.

Change re-exportation requirements.

Our working plan is to build a coalition of other companies with a vested interest in changing the re-exportation restrictions. We will be working with Senator Hatch and other key congressional leaders to craft new legislation and place pressure on DEA senior management. Note that there will be a change in DEA leadership during 4Q00, and that this new leadership is believed to be more open to addressing our issues than previous staff.

This project will be led by Scott Melville of Cephalon's legal department. It is anticipated that the coalition will be organized by year end 2000, enabling introduction of legislation during 1Q2001.

Costs will include consultants and travel and may take 2 years to reach resolution. If successful, *Actiq* costs for Europe could be significantly reduced.