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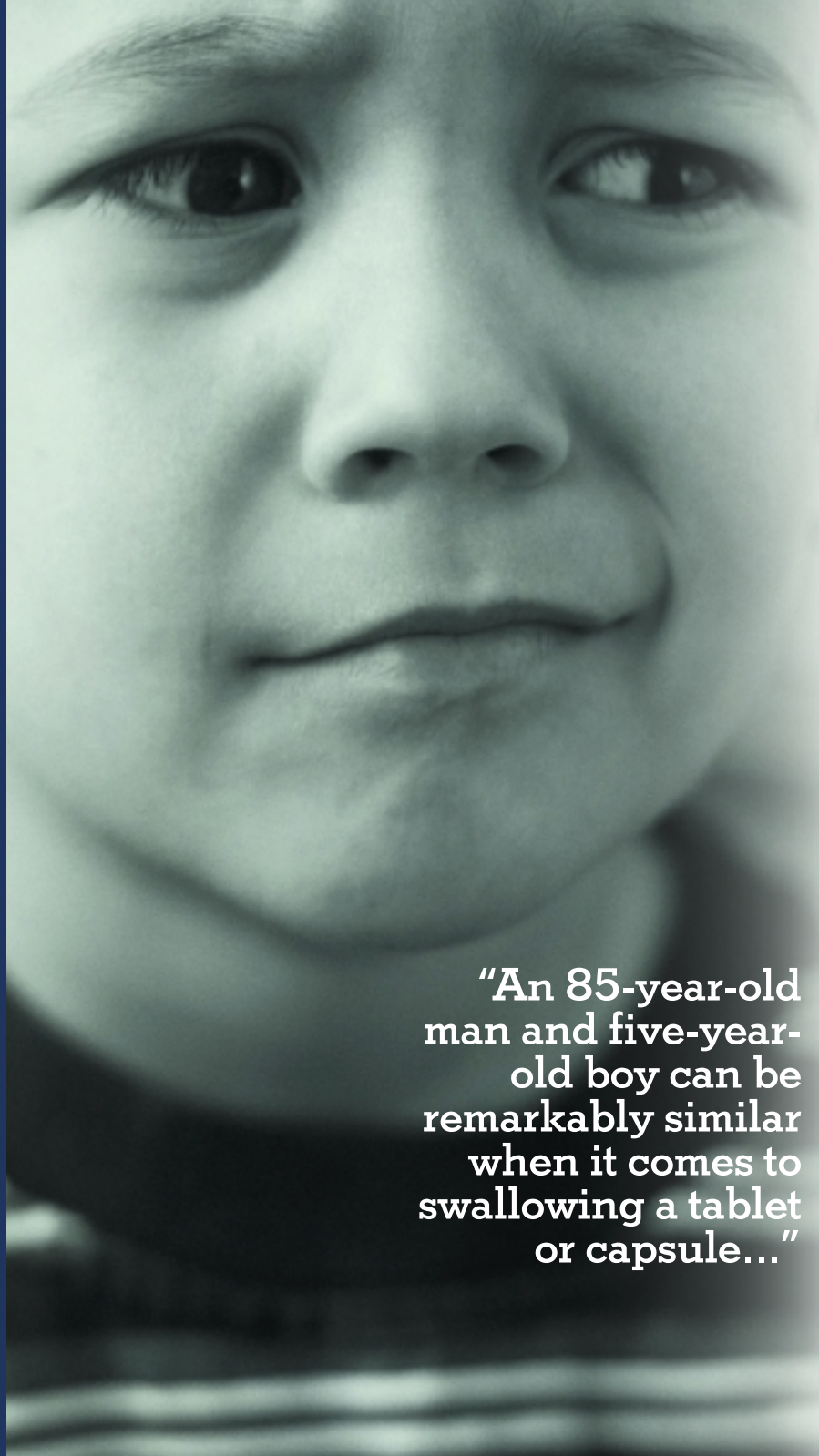
Swallowing a bitter pill.

Limited availability of oral liquid pharmaceuticals causes patient suffering.

BY **Sarah Adams**



"An 85-year-old man and five-year-old boy can be remarkably similar when it comes to swallowing a tablet or capsule…"

FOR CAREGIVERS IN PEDIATRIC WARDS and nursing homes it's a daily challenge to get patients to take their medicines: Tablets must be crushed into smaller pieces and capsule contents mixed with food or disguised in beverages. Difficulty swallowing tablets and capsules is common for these populations. Surprisingly, this problem also affects the general adult population. A recent survey conducted in the UK found that 63% of cancer patients and 48% of non-cancer patients under medical care reported swallowing difficulties.

The widespread practice of altering medications is easier for caregivers but raises significant ethical, legal and pharmacological issues. Many solid dose forms may be especially hazardous when crushed.

Opening or breaking medicines with carcinogenic properties can alter delivery mechanisms, release unwanted airborne particles and may cause cytotoxic activity. When modified-release preparations are crushed or broken patients can receive an initial overdose, followed by a long period without medication. Or the medication may be rendered useless. There's really no way to gauge what's being administered.

No Alternatives

This risky practice continues because no good alternatives exist. Patients might benefit from an oral liquid dosage form, but the economic realities of bringing oral liquids to market have historically been less attractive than solids.

"The US is more convinced than other countries that tablets and solid dosage forms are the best way to deliver medications," says Stephen Tarallo, president of Lyne Laborato-

ries, a manufacturer that specializes in oral liquid pharmaceuticals. "In Europe, oral liquids are used quite often. Suppositories are also a very popular delivery system, as are unit-dose, metered nasal sprays and drops. It's only the US that's so single-mindedly focused on solid dose. Convenience is a very important attribute in the US market and tablets are definitely seen as more convenient."

From a manufacturing standpoint, tablets are generally faster and less expensive to produce because liquid formulations are more fragile and the chemistry is more difficult to negotiate through the development maze. Contamination and stability are greater concerns for liquids since active materials have a greater propensity to break down in liquid.

None of these issues are insurmountable, Tarallo says. A high level of scientific expertise in handling liquids and complete diligence and quality control in manufacturing are all that is needed. Liquids offer faster absorption into the system and the ability to carry a higher dosage. In the final analysis, however, if liquids are the only way a patient accepts the medicine, these properties become secondary issues.

Incentives for Oral Liquids

Even though tablets are less expensive and faster to make, there are strong incentives to pursue oral liquids. Traditionally, pharmaceutical companies have pursued oral liquids only out of necessity. Certain medications can only be delivered by liquid because of a very high dosage level or particular characteristic of the active ingredient. Liquids are mandatory for certain target markets, like infants. Yet when an oral liquid formulation extends a pharmaceutical company's product line or product life cycle while potentially garnering additional patent exclusivity, the decision to pursue an oral liquid dosage form is based more on business than patient need.

"The pharmaceutical community is really reluctant to develop an oral liquid product to treat only 4,000 or 5,000 or even 10,000 kids a year," says Emmett Clemente, MD, former chairman of Ascent Pediatrics. "The economics aren't there. Pediatric products are always an afterthought, rarely a primary business." To support this statement, Clemente cites cephalosporin antibiotics, a common type of antibiotic that was extended into pediatric application. In the adult market one product can generate hundreds of millions of dollars, but pediatrics is only a $25 to $40 million market. "Companies don't pay attention to oral liquids unless they have to or unless they have a significant stake in the adult market and the pediatric application would benefit them competitively."

Clemente knows firsthand how powerful the pocketbook can be in determining which dosage forms to develop. Ascent Pediatrics, now a subsidiary of Medicis Manufacturing Corp., focused on addressing the unmet needs of children through the development of differentiated, proprietary products based on approved compounds with well-known clinical profiles. The steroid Orapred (prednisolone sodium phosphate, oral solution) is an example of a product developed by Ascent for children with asthma and other inflammatory conditions unwilling or unable to take their medication. Because the oral liquid steroid market, which is mainly aimed at pediatrics, totals approximately $50-60 million, pursuing it is only attractive to a dedicated pediatric company.

Significant Future?

In the future, patient preference for oral liquids may become a more significant driver. Oral liquids may benefit from recent regulatory and market developments. As an economic incentive, FDA's 1997 provision extending exclusivity for six months or offering patent protection for conducting pediatric studies has generated more clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.

"FDA understands that the obstacles that exist create a disincentive to serve the pediatric population. The agency needed to do something to stimulate and reward the development of pediatric medicine," says Clemente. For many pharmaceutical companies, the exclusivity provision justifies the expense of providing the small but underserved pediatric community with new medications and appropriate dosage forms, such as liquids, and new labeling. To date, 73 products have been granted exclusivity and 49 have received new labeling.

Growing Geriatric Population

The rapidly expanding geriatric population may also be a boon for oral liquids. In 1999, 600 million people were aged 60 years and older worldwide. By 2050 that number will jump to almost 2 billion, at which time there will be more elderly people than children (0-14) for the first time in human history. One of every five people will be older than 60, with 19% of that population older than 80. The number of centenarians will likely increase 15-fold to 2.2 million.

Based on these statistics, pharmaceutical companies that respond to market demands for new medicines and appropriate delivery systems such as oral liquids stand to reap economic rewards. The geriatric sector will be particularly appealing because of the dependence of many geriatric patients on lifestyle drugs or daily medications.

"An 85-year-old man and five year-old boy can be remarkably similar when it comes to swallowing a tablet or capsule," says Tarallo. "You can't reason with them on the grounds that it's good for them. If it's hard for them to swallow the medicine, the chances that they'll take it and receive adequate care are diminished. That's why oral liquids make sense. Virtually everyone can take them."

In addition to geriatric and pediatric populations, patients on combination chemotherapy for metastatic breast cancer, esophageal and stomach metastasis and radiotherapy have swallowing difficulty. Esophagitis and swallowing difficulty following post-mastectomy radiotherapy may occur in approximately 20% of treated women.

"If you look around there are lots of patient populations that would benefit from greater access to oral liquid pharmaceuticals," says Clemente. "Liquids may always be a smaller niche than solid dosage forms, but we might be coming to a point where, because of increased patient demand, they are more viable for companies to pursue. If all things were equal, and economics weren't the primary driver, I know there would be a lot of liquids out there."

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