

# Appendix A: Major Studies of Pharmaceutical Labeling in Developing Countries

The 1970s marked the rise of the consumer movement and a time of increased attention to the operations of multinational corporations (MNCs) in developing countries. Concern was growing that many MNCs operated in a virtually unregulated environment in developing countries, in some cases to the detriment of consumers. A number of consumer groups, health care workers, and representatives from international organizations raised concerns about certain corporate practices in developing countries. One issue raised with respect to pharmaceutical companies was the quality of their prescribing information. Small studies began to disclose that a number of pharmaceutical MNCs had labeling standards for developing countries that differed from those for industrialized nations. These studies are discussed below.

## IOCU: The Chloramphenicol Study

The first comprehensive study of pharmaceutical labeling in the developing world was carried out by member groups of the International Organization of Consumers Unions (IOCU) in 1972 (16). IOCU examined 55 packs of chloramphenicol marketed by MNCs in 21 countries. Chloramphenicol is an antibiotic that can cause aplastic anemia, a serious blood condition. Although aplastic anemia is rare, when it does occur it has a fatality rate of 40 percent or more (210). Since the discovery of this connection in the 1950s, use of chloramphenicol has been limited in the United States and other industrialized countries to treating serious infections when alternative treatments failed. IOCU did not find a single label that included

all the necessary contraindications, and they found wide variation in the warnings given with identical brands sold in different countries (34,61).

## IOCU: The Clioquinol Study

A larger study was done during 1974 and 1975 on clioquinol, a drug originally introduced for treatment of amoebic dysentery, but often used for treatment of traveler's diarrhea (53). By the early 1970s, clioquinol was implicated in an epidemic of subacute myeloptoptic neuropathy (SMON), an often fatal condition that causes blindness and paralysis. The epidemic claimed the lives of about 10,000 people in Japan. As a result, where it was still available, clioquinol was recommended only for treating acrodermatitis enteropathica, a serious chronic condition affecting the skin and bowels of young people.

At the time of the study, clioquinol had been banned in the United States and Japan, and was available only from a pharmacy in Norway, Sweden, Austria, Finland, France, Iceland, Italy, the Netherlands, Yugoslavia, New Zealand, some places in Australia, the Philippines, and Denmark. It was available without prescription, but in most cases only from a pharmacy, in the United Kingdom, Belgium, Ireland, Guatemala, Ghana, South Africa, Tanzania, Egypt, Lebanon, Zambia, Malaysia, Mexico, Sri Lanka, Israel, Greece, Tunisia, Thailand, Taiwan, Iraq, and Brazil.

The IOCU researchers obtained 107 drugs containing clioquinol from 39 countries, of which 83 samples from 34 countries included package inserts. Almost all of the package inserts recommended the drug for

the treatment of diarrhea and 50 of them recommended it as a prophylactic. The indications were often vague, e.g., “for specific medically indicated prophylactic use.” The dosage recommendations on 63 leaflets ranged from 400-1,500 mg per day for 3 to 28 days, despite the fact that the clinical literature recommended an adult dose of only 750 mg a day for 14 days (169). Twenty of the leaflets had no recommended dosage, Thirty-two leaflets mentioned the most important contraindications: hyperthyroidism, iodine allergy, and malfunctioning of the liver or kidneys; however, 37 leaflets listed no contraindications, including those from the United Kingdom, New Zealand, Belize, Brazil, Tanzania, Taiwan, Kenya, Spain, Malaysia, and Singapore. One explanation offered for the lack of contraindications on certain of these package inserts was that the insert recommended a maximum treatment of 3 days, after which it recommended consulting a doctor if the diarrhea was not cleared up. The risk of an adverse effect from clioquinol was relatively small if used in low dosage for a few days.

Information on side effects was also analyzed. Forty-five leaflets listed the major side effect, peripheral and optic neuropathy, but only 34 recommended stopping the drug at the first sign of peripheral neuritis or optic neuritis. The researchers concluded that warnings were deficient on inserts from the United Kingdom, Bahamas, Belize, New Zealand, Brazil, Indonesia, Thailand, Tanzania, Taiwan, Iraq, Kenya, Malaysia, and Singapore. However, the lack of complete warnings in the United Kingdom, Belize, Bahamas, and New Zealand was tempered by the fact that there were instructions that the drug be taken for no more than 3 days,

The study also looked at four other halogenated hydroxyquinoline drugs (the same chemical class as clioquinol) because there was some evidence that these drugs also could cause neurological illness. The researchers examined 44 leaflets from 24 countries. Again, there were many differences in indications, contraindications, and warnings on the package leaflets. There were differences among labels within the same country and among labels provided by the same manufacturer for a drug marketed in different

countries. Some of the differences might have been attributable to different national regulations, but the differences within countries indicated that differing regulatory requirements were probably not the sole explanation. A number of lawsuits were brought against MNCs that marketed products containing clioquinol (primarily Ciba-Giegy, a Swiss company, and Takeda and Tanabe from Japan), Damage awards eventually reached almost \$900 million.

Today, clioquinol is banned in the United States and United Kingdom, and in other industrialized and developing countries. However, a recent study found many products containing clioquinol in India, Indonesia, **Thailand, the Middle East, Egypt, Mexico, Central America, Colombia, Venezuela, and Brazil**. A number of these products are marketed by domestic companies and their labeling carries little or no warning of possible neurological damage. Despite clioquinol’s history, it is considered safe and effective in a number of developing countries, and in India is considered an essential drug (212).

### **IOCU: The Anabolic Steroid Study**

In 1983, IOCU released a study about the marketing of anabolic steroids in Germany, Australia, the United Kingdom, the United States, and a number of Asian countries (118).<sup>1</sup> According to the cited clinical literature, anabolic steroids were recommended only for treatment of certain serious anemias resulting from bone marrow failure, and for treating osteoporosis in the elderly. Anabolic steroids were also recommended for children with certain growth disorders, but because they can cause subsequent infertility, precocious or abnormal sexual development, and stunt growth, this indication was very limited. Other known side effects of anabolic steroids include irreversible symptoms of masculinization in women (deepening of voice, body hair growth, male-pattern baldness), and in men, atrophy of the testicles, inhibition of sperm development, and impotence. Anabolic steroids were also linked to liver tumors, jaundice, acne, and nausea.

IOCU examined 38 anabolic steroid products marketed in Indonesia, Bangladesh, the Philippines,

<sup>1</sup> *This* was not the first study to examine the labeling and marketing of anabolic steroids in developing countries. See also references 134,163,208.

Thailand, Mexico, Malaysia, the United States, and West Germany. Fifteen samples came from a single Dutch company, Organon, and the remaining drugs were marketed by Winthrop, a U.S. company, and Schering, a West German company, Package inserts, advertisements, and other promotional literature were examined.

The study found examples of these companies marketing the same product with complete warnings in developed countries and less-than-complete warnings in developing countries. Anabolic steroids were promoted in the developing countries for poor appetite in children, poor weight gain, listlessness, and lack of energy, sometimes using pictures of healthy, well-nourished children. In a number of countries, the drugs were available in easy-to-take drops and syrups, often flavored to make them more palatable to children. Package inserts in Bangladesh and the Philippines stated specifically that there were no contraindications in children. Another 16 package inserts failed to caution against use in children or to recommend that skeletal maturation be checked periodically by x-ray. A majority of the package inserts also failed to warn against use in patients with kidney or liver disease.

Side effects were also minimized. Nine package inserts *from* developing countries listed no side effects. The majority of products that did include warnings about side effects failed to warn against impotence, enlargement of breasts, liver damage, jaundice, or the more common side effects found in children,

### The Yudkin Study

In the late 1970s, a British physician, J.S. Yudkin, compared the prescribing information in the African Monthly Index of Medical Specialties (MIMS)<sup>2</sup> with information on the same drugs in the British MIMS (292). He found significant discrepancies in indications and warnings. For example, tetracycline was marketed in Africa with no warning about the risk of tooth discoloration in children. In Britain, anabolic steroids, whose side effects include stunting of growth, virilization (appearance of secondary male sexual characteristics in women) and liver tumors, were rec-

ommended only to treat osteoporosis, renal failure, terminal malignancies, and aplastic anemia. In Africa they were also indicated for treatment of malnutrition, weight-loss, as appetite stimulants, and for excessive fatigue. In the African MIMS several different brands of liothyronine, a drug recommended for "severe thyroid deficiency" in Britain, were marketed for "low-ered metabolic states." Methadone, which was recommended in Britain for severe pain, was marketed in Africa as a cough suppressant.

### The Social Audit Studies

A 1978 study by the British consumer group, Social Audit, funded principally by IOCU, focused on products of the major British pharmaceutical MNCs: Beecham, Boots, Fisons, Glaxo, ICI, Reckitt and Colman, and Wellcome (142). The study compared the information from British MIMS with MIMS guides from Africa, the Caribbean, and the Middle East. When available, the researchers also looked at detailed prescribing instructions in India and Malaysia. They found that dosage recommendations in developing countries tended to be greater, even double the dosages recommended in the United Kingdom. The study also found a marked lack of detail about contraindications. For example, the British official prescribing information for Ancoloxin (meclizine), an antiemetic, warned against use in pregnant women except in cases of severe vomiting. U.S. labeling also warned against use during pregnancy because animal studies had indicated the drug might cause birth defects. However, in Africa and some developing countries in other areas, it was indicated specifically for the treatment of nausea and vomiting in pregnancy. Even the detailed prescribing information in India did not contain warnings about potential birth defects. Another example was the painkiller, Paramol 118 (dihydrocodeine). In Britain this drug required warnings against use by children, people with impaired liver or kidney function, or during an asthma attack. This same drug was marketed in Africa without these warnings.

In contrast, indications were often more expansive in the developing country guides than in the U.K.

<sup>2</sup>MIMS are commercial prescribing guides distributed free to physicians. Their prescribing information is supplied by the pharmaceutical manufacturers and edited by the publishers. Production of the guides is paid for by advertisements.

MIMS. For example, a painkiller marketed in the United Kingdom for “persistent pain, particularly muscle pain, headache, neuralgia,” was indicated in Africa and the Caribbean also for “fibrosis, lumbago, back pain, sprains, strains, dysmenorrhoea, dental pain, bursitis, trauma, and chronic rheumatic pain.” While this detail was not necessarily misleading, the researchers concluded that the emphasis in indications coupled with deficient warnings demonstrated that the companies were more interested in drug promotion than in providing objective prescribing information. The researchers found that the quality of information did vary by prescribing guide and by company, but because no attempt had been made to obtain a representative sample from each company, no comparative analysis could be carried out.

### Silverman, Lydecker, and Lee’s Studies

Some of the most comprehensive and influential research on drug labeling in developing countries was carried out by U.S. researchers. In 1974, Silverman and Lee, of the University of California in San Francisco, published *Pills, Profits and Politics* (209), which focused on the policies of both U.S. and foreign pharmaceutical manufacturers and included evidence that these companies provided irrational prescribing information. Further work was published by Silverman in *The Drugging of the Americas* (208), which examined the prescribing information for 26 single-drug entities or fixed combinations, marketed by 23 MNCs as 147 different products in 12 countries in Central and South America (212).

The drugs in this study included antibiotics, oral contraceptives, nonsteroidal antiinflammatory drugs, steroid hormones, antipsychotic tranquilizers, antidepressants, and anticonvulsants. Each drug selected met the following criteria:

- it was a valuable and widely used drug;
- it had well-established clinical usefulness and known hazards;
- it was marketed in the United States and Latin America by the identical company, its foreign subsidiaries, or affiliates; and
- it was described in the U.S. *Physicians’ Desk Reference* (PDR) and selected prescribing guides in Mexico, Central America, the Dominican

Republic, Ecuador, Colombia, Brazil, and Argentina.

The PDR, which contains the labeling information approved by the U.S. FDA, was used as a standard. The researchers concluded that “with few exceptions, the indications included in the Latin American] reference books are far more extensive, but the listings of hazards are curtailed, glossed over, or totally omitted” (208). There also were examples of the same drug marketed by the same company with different information in different countries. One of these was chloramphenicol. The PDR recommended chloramphenicol for acute typhoid fever only, and to treat serious cases of salmonella, hemophilus influenza, some types of meningitis, and some forms of cystic fibrosis. In addition, the drug was not recommended for infants, pregnant women, or in patients in whom there was evidence of hypersensitivity, depression of bone marrow, signs of blood dyscrasia (abnormalities in the production of blood cells), or impaired liver or kidney function. Potential adverse reactions included aplastic anemia (which may be fatal), blood dyscrasias, nausea, vomiting, headache, mild depression, mental confusion, and other necrologic reactions. The PDR also recommended that periodic blood studies be done on patients taking the drug to avoid the most serious reactions.

The study examined five brands of chloramphenicol marketed by four companies in Latin America, including one brand that was removed from all markets in 1973. All the prescribing entries evaluated included broader indications than those in the PDR. The antibiotic was recommended for dysenteric infections, tonsillitis, colitis, whooping cough, and as a broad-spectrum antibiotic. The prescribing guides for Central America, Argentina, and Ecuador contained no contraindications or warnings. In other prescribing guides, the warnings and contraindications were limited. Listings for three of the brands, taken from four different prescribing guides, failed to warn against aplastic anemia or other blood dyscrasias.

Oral contraceptives were also examined. The PDR lists many contraindications, the most important being thrombophlebitis, impaired liver function, known or suspected estrogen-dependent malignancies, and unexplained abnormal genital bleeding. Many adverse reactions were also presented, including changes in li-

bide, nervousness, dizziness, loss of hair, and skin changes.

Again, Silverman found prescribing guide entries with far more indications than in the PDR. Entries for seven different oral contraceptives, marketed by five multinational corporations, recommended oral contraceptives for premenstrual tension, uterine bleeding, and various menstrual disorders. Thrombophlebitis was included as a contraindication in 14 out of 20 entries; suspected hormonal neoplasms in 4 out of 20; undiagnosed abnormal vaginal bleeding in 4 out of 20; emotional disease in 2 out of 20; and caution in cases of epilepsy, migraine, asthma, or cardiac or renal dysfunction was included in only one entry. Eleven entries listed no potential adverse reactions.

In *Prescriptions for Death: The Drugging of the Third World* (210), Silverman, Lee, and Lydecker returned to Latin America, but expanded Silverman's earlier work to include Central Africa (15 countries), Southeast Asia (4 countries), and the United Kingdom. The researchers examined 515 prescribing guide entries for 34 drug entities or fixed combinations marketed by more than 149 companies (46 were products of U.S. multinationals or their affiliates) (211). They examined many of the same drugs they had looked at in *The Drugging of the Americas*. This 1980 study again showed that certain prescription drugs were promoted in developing countries for more indications than had been approved in the United States and that mention of serious adverse reactions had been minimized or omitted from the labeling.

In Indonesia, Singapore, the Philippines, and Central America, chloramphenicol was still recommended for minor infections such as bronchitis, vaginal infections, and throat infections, and that almost all of the chloramphenicol products marketed in Indonesia had no warning about aplastic anemia. A number of products marketed in the Philippines, Malaysia, and Singapore also failed to mention aplastic anemia or had no warnings at all. In the African MINIS, however, which had been critiqued just a few years earlier by Yudkin, the authors found information almost identical to the PDR.

The authors looked again at tetracycline drugs, which are not recommended for most patients with impaired liver or kidney function. In infants and young children, tetracycline may discolor teeth and interfere with bone growth, so it is not usually recom-

mended for women in the last half of pregnancy or for children under the age of 8 or 12. Of the 90 tetracycline products examined from developing countries, warnings about use in patients with kidney disease were given for 13; warnings about use with liver disease, for 9; and about use during pregnancy, for 9. Thirty-five products had no specific warnings, though some included vague warnings or referred the prescriber to the literature (210).

The study also analyzed prescribing information for certain combination antibiotics, clioquinol, dipyrone, and oral contraceptives. The investigators found that the dangers of serious or lethal side effects were frequently minimized or totally ignored, and claims of effectiveness often "wildly exaggerated" (210).

In 1984, Silverman, Lee, and Lydecker published the results of another survey. The 1984 study examined information from prescribing guides for 63 drug entities or fixed combinations, marketed as 1,069 different products by 303 drug companies in 15 countries (211). The study revealed that a number of pharmaceutical companies had made a "marked improvement" in their promotional and labeling practices in developing countries. The authors examined 103 chloramphenicol products and found that 93 carried warnings against use in trivial infections, for prophylaxis, or in prolonged therapy. They also examined the prescribing entries for 117 tetracycline products, and found that 109 carried suitable warnings, including contraindications for kidney and liver disease.

With respect to dipyrone, a pain reliever that was withdrawn from the U.S. and British markets because it could cause agranulocytosis, a fatal blood condition, the authors found that 119 out of 155 (76 percent) contained warnings of serious or possibly fatal agranulocytosis. In 1980, only half of the dipyrone products studied warned about agranulocytosis.

Clioquinol and the related halogenated hydroxyquinolines, which had previously been promoted as anti-diarrhea agents, were also studied. Twenty-two out of 61 prescribing entries for products containing clioquinol failed to include warnings of severe and possibly fatal neurological damage. They concluded that most cases of irrational promotion (60 percent) involved domestic firms in developing countries. They cautioned that the "problem of irrational, inaccurate, or even dishonest promotion has not been solved" (211).

During 1987 and 1988, at approximately the same time OTA gathered its labeling material, Silverman, Lydecker, and Lee revisited the issue of drug labeling in developing countries, this time with partial financial support from 10 pharmaceutical companies. The researchers examined 40 single-drug entities or fixed combinations marketed as 1,500 products in the United States, the United Kingdom, and 74 developing countries—28 countries in Africa (both English and French speaking), 12 countries in Latin America, 11 countries in the Caribbean, and 6 countries in Southeast and southern Asia (212). The products were marketed by more than 400 companies, both MNCs based in industrialized countries and domestic companies in the developing countries.

The drugs chosen for the study were in the following categories, including many of the same drugs they had examined in previous studies: analgesics, antiarthritis drugs, antidiarrheals, antibacterial, appetite stimulants, cardiovascular drugs, cerebral vasodilators, psychoactive agents, major and minor tranquilizers, antidepressants, anabolic steroids, female sex hormones, and sex potions. As in their previous studies, prescribing guide entries were analyzed. Unlike the OTA study, Silverman and his colleagues focused on certain indications or warnings for each drug, rather than examining the entire label. The results of their study were published in the spring of 1992.

The authors concluded that most multinational corporations were willing to disclose major hazards and to limit their indications to those based on sound scientific evidence; there were, however, “glaring exceptions.” They found that the total amount of misinformation presented to physicians had not changed because the improvements made by the multinational corporations appeared to be offset by the misleading labeling presented by the increasing number of local or domestic firms (212).

### The UNCTC Study

In 1984, the U.N. Centre for Translational Corporations published a study that included a section on drug marketing by MNCs in developing countries, examining 12 products marketed in 12 countries. Each drug selected had some significant side effect or contraindication. The review found “significant discrepancy[ies]” between the information provided in the PDR and the information provided in the prescribing

guides of Brazil, Colombia, Ecuador, Mexico, Venezuela and Central America. For example, clofibrate, a cholesterol-lowering drug, has some serious side effects, including gallstones, leukopenia (decreased production of white blood cells), and cardiac arrhythmias. In Brazil, Ecuador, and Mexico, the prescribing guide did not mention any of these effects. In Argentina, one MNC marketed 17 varieties of clofibrate with no mention of side effects, although the same firm sold the drug in the United States with complete side effect and warning information (223).

The study also looked at prescribing guide entries for five drugs containing dipyrone, a pain reliever that can cause a fatal blood disease. The United States had banned the drug, as had Australia, Sweden, and the United Kingdom, but it was still on the market in some European countries as an analgesic, antipyretic, and antispasmodic. The study found that dipyrone was widely used as a general painkiller in Brazil and Argentina, often without prescription or proper warning. In Thailand, the drug was dispensed over-the-counter more often than aspirin. In Costa Rica and Kenya, it was an ingredient in many popular medicines. A review of the prescribing guides found a number of entries promoting the drug for treatment of headaches, common cold, pneumonia, and rheumatoid arthritis. In some cases, the risk of the fatal blood disease was mentioned, but no mention was made of the need for hematologic tests to detect its onset early. Other entries mentioned no side effects. The U.N. study also cited a review by two researchers of 110 antibiotic preparations marketed in Central America. According to that study, prescribing guide entries for 40 of the preparations had no information on contraindications and 66 had no information on adverse reactions (79).

The U.N. study concluded that in most of the countries studied there were no limits on the amount of information that could have been provided. However, the study also noted that some companies had begun to respond to the criticisms with promises to dispense uniform labeling information and to support standard international drug prescribing information (223).

### The Osifo Study

In the early 1980s, a small study was carried out in Benin City, Nigeria, to determine whether Nigeria’s new labeling regulations altered the content of pack-

age inserts (171). Nosakhare Guy Osifo, a pharmacologist, examined package inserts for 28 prescription drugs marketed by 15 U.S. MNCs or their subsidiaries. Osifo found that the four package inserts supplied with products exported directly from the United States were identical or very close to the U.S. labeling. The remaining package inserts, included with 18 different products distributed by U.S.-controlled foreign subsidiaries, contained more indications and fewer warnings than appeared in U.S. labeling. Inserts for drugs specifically for use in critically ill patients, which were generally more dangerous products, tended to be more complete and accurate than those accompanying products for less serious conditions.

### The Hartog and Schulte-Sasse Study

Hartog and Schulte-Sasse, two German physicians working with the support of BUKO-Pharmakampagne (a German public interest group that focuses on pharmaceutical issues) reported on more than 2,000 German and Swiss pharmaceutical products marketed in 26 developing countries (81).<sup>3</sup> The study, published in 1990, evaluated whether these drugs, mostly products of MNCs, met the health needs of the countries where they were marketed by comparing them with WHO's Essential Drug List. They also evaluated the efficacy and safety of all the drugs and examined labeling and advertising.

Drugs were classified as inappropriate if:

1. there were no efficacy data to support the labeling or advertising claims;
2. the available data had been criticized as scientifically inadequate by a substantial number of experts; or
3. different researchers reported contradictory results.

Even if a drug was found efficacious, it was deemed inappropriate if there was a more effective or less dangerous alternative. Finally, a drug was considered inappropriate if the amount of active ingredients was too low at the recommended dose, or the drug would fail to be effective as administered (e.g., the oral form of an antispasmodic, butylscopolamine, which is effec-

tive only as an injection). Using these criteria, the researchers concluded that more than 60 percent of the drugs evaluated were inappropriate.

The WHO Essential Drug List includes only drugs that are of "utmost importance and are basic, indispensable and necessary for the health needs of the population." The drugs also are selected on the basis of cost and the practicality of prescribing a particular medicine under a variety of medical situations (e.g., in situations where there is little likelihood the patient would be monitored). Hartog and Schulte-Sasse compared the products in their sample to therapeutic agents on the WHO list, looking specifically at ingredients, concentration, and dosage form. They concluded that less than 20 percent of their sample drugs would meet the criteria for inclusion in an essential drug list.

In the analysis of labeling, the study reported deficiencies in information in MIMS prescribing guides for English-speaking Africa and the Middle East, the Philippines, and India. They compared information in the Swiss pharmaceutical compendium with the developing country prescribing guides. They concluded that the prescribing guide entries typically included more indications and less information on adverse effects and contraindications than did the Swiss compendium.

### The Industry Response

Industry responses to these studies have varied. The International Federation of Pharmaceutical Manufacturers Associations claims that companies quickly responded to *The Drugging of the Americas* by developing internal corporate policies to guarantee that claims about efficacy and disclosures about side effects were consistent worldwide (37). Some companies blamed MIMS editorial policies for discrepancies between the official drug datasheets and MIMS entries. Companies also noted that MIMS guides were not the sole source of information for physicians, and that their company representatives did provide complete information, or that information was available from the company on request (210).

<sup>3</sup>The study looked at 1,312 German products marketed in 1984/1985, 1,273 German products marketed in 1988, and 1,084 Swiss products marketed in 1988.

The primary explanation offered by companies for the differences between the information given in developing and developed countries was that developing countries had different laws and regulations. As a former President of the U.S. Pharmaceutical Manufacturers Association (PMA) explained shortly before the release of *Prescriptions for Death: The Drugging of the Third World*, “our foreign labels conform to the labeling regulations of the importing country which may forbid the sorts of disclosure required by the FDA” (148). Another PMA representative stated that it would be arrogant and paternalistic to insist that one nation’s decision in the area of drug regulation was superior to another’s (165),

Critics pointed out that regulatory policies were not responsible for the labeling differences between industrialized and developing countries. As evidence of this, they noted several examples where, in a single country, the same chemical entity was marketed by different companies with substantially different labeling. Also, since the information in most of the prescribing guides was not regulated by the host governments, the critics contended that regulatory policies were not responsible for the differences found in the guides.<sup>4</sup>

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<sup>4</sup>See, e.g., references 62,134,142,148,154,260.