Chloramphenicol is not aligned with drug interaction, therefore, when given to patients together with anticoagulants or anti-congestion drugs, an adaptation to these might be necessary.

Adverse reactions:

Blood dyscracias and even aplastic anemia with fatalities in rare occasions have been associated with the use of chl. Dry mouth, nauseas (less frequent) and occassionally diarrhea or vomit are present but they rarely are as severe as to justify the suspension of the antibiotic. Sometimes cases of sensitivity reactions are found.

Doses:

For adults and children is calculated on the basis of 50 mg per kg. of weight per day, at 6 hours intervals, equiv. to 2 or 4 capsules or spoonfuls of suspension.

For prematures and newly born babies, less than 2 weeks old the dose should be reduced to 25 mg ch. per kg. of weight daily. Physiological immaturity of these children is the cause of this reduction. More information about this matter is given in the monography of the product, under the title "gray syndrome".

In the pre-operatory stage this dose can be used during 3 or 4 days before the intestinal surgery. Chlorostrep is particularly useful in the post operatory stage, together with liquids via oral. In cases of pathogen infection the treatment should be continue during 5 or 6 days. When used for annal fistula tuberculosis larger doses should be given increasing it or following a scheme more prolonged. In cases of renal insufficiency the ability to metabolize or excrete chl. can be reduced, and the physician should adjust the dose consequently.

Packing: In containers with 8 capsules and in flasks of 60 cc. liquid.

FOR COMPLETE INSTRUCTIONS ON THE PRESCRIPTION, CONSULT THE MONOGRAPHY AVAILABIE AT REQUEST FROM THE PHYSICIANS.

PARKE DAVIS
Laboratorios Parke Davis S.A.E.
MADRID

5-PM

Control of Medicines in Spain

14. Control of medicines in Spain asperceived by Mr. and Mrs. Zander after personal interviews in Spain with two physicians and two officials.

CONTROL OF MEDICINES IN SPAIN

Our Parke-Davis Company in defending its product information on Chloromycetin when it is sold abroad always stresses that the company follows the rules of the health regulatory agency of the country in which it is selling its product, explaining, however, that "regulations on sales are less strict in some countries and some even limit the labeling", implying that in such countries the health regulatory agency, not Parke-Davis, is responsible for lack of adequate warnings on their labels. They also advised us to talk to physicians abroad to get their views of Parke-Davis labels for use of Chloromycetin in their own country. At the end of September 1973 we spoke to doctors and health regulatory officials in Spain on the subject. We chose Spain because Parke-Davis chloramphenicol labeling in Spain in the past has been lacking in warnings of fatal aplastic anemia and has encouraged unnecessary use in comparison with the company's U.S. Chloromycetin label and, since it now has the new Parke-Davis Chloromycetin Monograph of basic product information and a new label, a substantial improvement but still inadequately strong in warnings and use restrictions. Also, we have the most documented materials from Spain since it was there that our daughter may have been given chloramphenicol for tonsilitis that may have been the cause of her death from aplastic anemia.

Our belief that the Parke-Davis Chloromycetin labels most lacking in warnings and encouraging in unnecessary use were precisely in those countries with the weakest health regulatory agencies as exemplified in our collection of labels from various countries, was corroborated in the case of Spain by our talks with physicians and health regulatory officials. In the past, at least, if Parke-Davis had pushed to include strong warnings of fatal aplastic anemia and to restrict unnecessary use, especially for relatively trivial illnesses, when it was required to do so in the U.S., we are convinced that it could have done so in Spain.

We first had lengthy conversations with two physicians in Spain who felt so strongly and were so outspoken to us on the past weakness of their country's health regulatory agency and the power of strong pharmaceutical companies to do as they wished in pushing the sale of their product and also the consequent ignorance of Spanish doctors in general in prescribing medicines that, considering the present political climate in Spain, we do not think it wise to identify them other than to say they are well-trained and experienced in the medical disciplines required to make such judgments. We will identify them privately but have a real concern for their safety because they are so impassioned in their criticism of their country in this respect. Attached are some notes on these conversations written immediately afterwards with identifying items hopefully removed. These physicians had detailed documentation of the inadequacy - and worse - of the information on use of their products given to the medical profession by the pharmaceutical companies.

Then we had a cordial interview with the Director of the Division of Antibiotics and the Director of the Division of Chemical Analysis of the Spanish Centro Nacional de Farmacobiologia (Control of Medicines). They also said that in the past the problem of control of medicines in Spain had been severe due to lack of funding and manpower so that powerful pharmaceutical companies did more or less as they wished and acknowledged that chloramphenicol had been too widely used in Spain. However, right now they were very excited and hopeful with the appointment of well-qualified Directors of Health and of CNDF which was being thoroughly reorganized, given more funding, and a four or five-fold increase in staff. Indications of the change are seen in their new chloramphenicol basic information that is much more restrictive of use, the requirements for all companies producing it to comply to these basic ideas in their labels (not sure they are able to carry this out fully), their beginning to use the World Health Organizations Adverse Reactions reporting system, the beginning of a drop in use of chloramphenical. However, they still do not have the manpower and are powerless to control advertising and promotional materials of the pharmaceutical companies including their Spanish publications comparable to our Physicians Desk Reference, and to recall old-labeled medicines when the label is changed (five years for chloramphenicol). Attached are notes on the conversation with these official.

Both the physicians and health regulatory officials to whom we talked in Spain gave us the distinct impression that in the past, at least, there has been very little effective regulating of the pharmaceutical companies and hence we believe that it was Parke-Davis itself that was responsible for the many years of inadequate labeling in Spain.

15. Notes on conversations with two Spanish physicians, September 1973.

Conversations with two Spanish physicians in Spain September 23, 1973:

Health, in Spain, is considered of a lower level of importance than in the United States as reflected in the fact that the national health agency, Direccion General de Sanidad, is only a section under the Ministry of the Interio and not a department of its own. Also it has in the past been and still largely is ineffective and worse, having been headed by political appointees, such as Franco's daughter's obstetrician (?) - rather than the best trained and best-qualified man. Also money interests and downright curruption (bribery) have controlled the health agency and in particular the Centro Nacional de Farmacobiologia (Control of Medicines) which corresponds to our FDA and which, in Spain, has been "just like the Mafia". The big moneyed pharmaceutical companies can get past laws and prevent laws and rules being passed by their power and bribery. Money rules, absolutely.

However, a year ago for the first time a good well-qualified man, Dr. Federico Bravo Morate, was appointed as Director of Health and another fine man, Dr. Manuel Reol Tejada, was appointed as head of the Centro Nacional de Farmacobiologia. So there may be some changes but the doctors we interviewed belive these two with the best will in the world cannot buck the entrenched powerful interests which have held sway so long and which fit into the whole miliue of Franco Spain. It was the super capitalists, the very rich, fighting the socialists - not Communists - in the Civil War annd they won. Spain has been ruled for their benefit ever since, in a very tight dictatorial system. There has been some easing up or he could not have been talking to us in this manner or doing the writing he is. But also there has been clamping down again recently, such as in the selection of the University president.

In this setting, the sale and use of medicines in Spain is ghastly. Anything to make money, both when some drug companies know what they are doing by omitting warnings, directly lying, and denying adverse effects, pushing use of dangerous drugs for all sorts of uses, making "shotgun" combination medicines of up to eight different drugs in one (perfectly incredible things all well documented by one of these physicians.) and also when they don't know what they are doing and through ignorance some companies, such as smaller "kitchen" drug companies , putting out potent medicines without scarcely any information on use. Advertising in freely distributed pharmaceutical companies "journals" fits the pattern of no warnings, even direct lies, push, push, push sales. The whole medicine picture he described is so awful it makes one afraid to put one self in the hands of a doctor in Spain. And the worst of it is, that from these two physician's point of view, it is all done because of greed. As one of the doctors said, only a few people they know in Spain, their close friends, think of money as what it should be "just a help to living"; to all the rest, nearly everyone, money is everything.

The difference in Spain compared to America, in their opinion, is that in the United States we still believe something can be done about it even though money is getting so powerful there (in U.S.) too, we can make changes. Here in Spain, it is impossible. One of the doctors says he is not a cynic when he sounds so hopeless; he is a stoic about the Spanish situation.

He said that Spain has no Public Health but it does have a National Health Service for all the people. However, there is much better private health care for those who can afford it. Two systems and that for the poorer people is definitely inferior. He cited an example of a distant relative of his who in the National Health Service was diagnosed as heart failure (?) but when he finally went to a private doctor, it was diagnosed as aplastic anemia from which he died. He said when National Health Service is as unreliable as this, it is obvious one cannot obtain reliable reports of incidence of aplastic anemia in Spain.

He mentioned a bare possiblity of a change for the better because he has heard that the big pharmaceutical companies are asking for stricter laws in labeling. He figures this is an effort to drive out the competition of little businesses but it may work to the good in terms of better labeling.

He said Parke-Davis's new Chloromycetin Monograph and label are good compared to the awful low Spanish standards in labeling but still not good enough for the best health of the people of Spain. When asked if the new label is "appropriate" for Spain, they said "appropriate" for Spain is not the right word since the Monograph and label

is "appropriate" to the present situation in Spain and in another sense it is not. They said the Monograph should be stronger, more like the United States label for the best health for the Spanish people.

The health regulatory agency does not require a recall of old-labeled stock, nor does it require warnings on advertising. He showed us horrible examples of such advertising which the health regulatory agency is unable to control.

One of the doctors also read to us an incredibly long list of all sorts of forms of presentation of a Mulk (?) product as an example of a very bad product, greatly pushed, and very much used. He spoke also of another very poor and dangerous product for the right to sell it, he knew that bribery had been involved, having heard certain orders given over the phone.

One of these doctors we interviewed has done a very painstaking study with many charts graphically portraying the inadequacies - and worse-of much of the product information supplied by the pharmaceitical companies. By going into this more fully in the notes, we are afraid that we might identify the author of this study and in the present political climate of Spain at the present (March, 1974) we have some concern for his safety since he is so outspokenly critical. Even in September when he thought the political situation had greatly improved in Spain, he said he could not testify publicly on these matters when he visited United States as it would not be safe for him in Spain afterwards. He is vitally interested in the problem of the low quality of the information given to doctors on use of medicines and has made a serious study of the situation. He has presented some of his findings to the fine new director of the Centro Nacional de Farmacobiologia who is a friend of his and who welcomed his documented information. He translated for us a description of chloramphenicol in a textbook which he had written and it had good strong warnings and use restrictions but this has not been typical of information on chloramphenicol in Spain. He also took down the book most widely used by doctors in Spain arranged by illnesses with recommended medicines for each illness and after "tonsilitis", there was "chloramphenicol". He says it is routinely and very widely used for tonsilitis and in his own mind feels sure that Judy must have been given it for tonsilitis when she was in Spain, that it would be the most likely thing she would be given. When we protested that he was supposed to be a University doctor, he said that would not make any difference.

The education of doctors in use of medicines in Spain is very poorly done by the pharmaceutical companies. The education of doctors in medicine in general even in the Universities shows great need for improvement. It is a pig problem. He said, though, the biggest problem is the doctors. They don't know and they don't care! If every doctor demanded full education in medicine, it would make the difference. He stresses that the doctors in Spain are at fault as well as the pharmaceutical companies or more so.

He said we could try to see officials in Madrid, the Director of Health and the Director of Drugs but that we should not expect anything to happen. But he feels our personal story may add a bit to the possibility of some little change.

One of the doctors said it would not be good for him to write an article just singling out chloramphenicol, that the broader problem is more important and a more effective way of attacking the problem.

Referring to a book by Weinstein, a top expert on infectious diseases in U.S., he said that in his discussion of aplastic anemia, he divides aplastic anemia into two types: one the hypersensitivity aplastic anemia, the other the toxic type. When he went on to say the hypersensitivity is just a theory but he feels there is something to it since chloramphenicol induced fatal aplatic anemia is not dose related, appears long after the dose (long time lapse), and has familial characteritics to a degree. This is what Parke-Davis and others refer to as the genetic theory. Our Spanish physician thinks the genetic theory explanation can be used as an excuse by the pharmaceutical companies for not giving aplastic anemia possibilities their due. He says it is just a theory but even if it should prove correct, there still should be full warnings etc. He said there may be something to the "race" 'genetic theory. Anglo-Saxons seem more susceptible than Mediterraneans though conceded the effect on apparent incidence due to more or less adequate reporting and records. He said certainly Spain has cases of aplatic anemia and cited his distant relative. Spain has quite a number of cases due to use of benzine in manufacturing.

16. Notes on interview with Chief of Antibiotic Division and Director of Division of Chemical Analysis of the Centro Nacional de Farmacobiologia (Control of Medicines), Madrid, September 1973.

Interview with Dr. Martinez Arroyo, Chief of the Antibiotics Division of the Centro Nacional de Farmacobiologia and Dr. Garcia Ferrandiz, Director of Division of Chemical Analysis of theCentro Nacional de Farmacobiologia: on September 28, 1973:

The interview withDr. Martinez Arroyo andDr. Ferrandiz was very cordial and conducted in English which may have occasioned some slight difficulties in understanding since it was not their mother tongue. The basic impression they left with us was that in the past in Spain the problem of control of medicines has been very severe. The Centro Nacional de Farmacobiologia (Control of Medicines) has been very weak, headed by political appointees with inadequate backgrounds, underfunded, understaffed. In this situation the powerful pharmaceutical companies did more or less as they wished and the physicians prescribed more or less as they wished. The CNDF just did nothave themanpower and funding to control the situation.

However, " at this moment" everything is changing: the new Director of Health, Dr. Federico Bravo Morate and the new Director of the CNDF, Dr. Jose Manuel Reol Tejada are very well- trained people, apparently for the first time. The staff of CNDF has been increased four or five-fold and there has been a total reorganization and they are moving to a much larger building. They sound very excited and hopeful of the future, readily admitting that though they have many improvements in the works at present, there are many things that they still cannot do all at once.

We were given a copy of the World Health Organisations Circular of the United States FDA-required Chloromycetin label and two brief statements of the CNDF's new basic position on use of chloramphenicol which, we believe, are used as a basis for the new chloramphenicol labels of all pharmaceutical companies. They are surprisingly restricted in the indications for use, much like our label, "surprisingly"considering past chloramphenicol labeling in Spain,but they do not have strong and full enough warnings of fatal aplastic anemia (perhaps because the Spanish officials themselves think that the Spanish people are not subject to this reaction, though in the past they have not kept records. They believe the fatal type is genetic and northern European peoples, especially Anglo-Saxons, are more subject to it. (yet they have 32,000,000 tourists each year, mainly from northern Europe). However, they have just begun with WHO record keeping of adverse reactions to medicines so that eventually there may be evidence to support or discredit their belief that Spaniards are not as subject to chloramphenicol-related aplastic anemia.

They readily agreed that chloramphenicol has been too widely used in Spain with much unnecessary use but said that use is beginning to go down, especially with the new medicines coming along, like ampicillin. They estimated that 80% of chloramphenicol in Spain is prescribed by physicians in the National Health Service with the other 20% private and sold over-the-counter with no prescription.

About our own Parke-Davis Company, they said that it is one of the smaller companies in Spain in selling its own product but said that Parke-Davis manufactures "tons" of chloramphenicol to sell to other Spanish pharmaceutical companies to market in Spain. They agreed that Parke-Davis Chloromycetin is a good quality medicine. They said the new Parke-Davis Monograph and label is , of course, not the same as the U.S. FDA-required label and indicated that they personally would like an even stronger label. They also said that they would not want United States companies to be required by the U.S. government to have the same labels in Spain as in the U.S. (the proposal the Project for Corporate Responsibility tried unsuccessfully to have adopted by the five major U.S. exporting pharmaceutical firms) but would want to require indluding fatal warnings etc. themselves. Parke-Davis has stressed that labels should be different in undeveloped and developing countries than in the United States but we had not thought Spain was in this category with countries like Columbia which Parke-Davis officials cited as an example. However, these Spanish health regulatory officials said that Spain healthwise actually was a developing county and implied it still is to a certain degree today while they are in this process of change. However, they did not go on to say that this justified past labeling of chloramphenicol, rather that it explained the poor labeling in the past in terms of the weakness of the health regulatory agency.

They said the CNDF does require the same warnings and use restrictions on all forms of a medicine marketed by a company when the basic label is changed as in the case with the Parke-Davis Chloromycetin label change this past year although we bought Parke-Davis chloramphenicol products of different forms of presentation while we were in Spain whose labels varied considerably. They explained this as due to old-labeled products still being available which were still within the five-year duration of effectiveness. In otherwords, they do not require the companies to recall their old-labeled madicines. They explained even now they still just do not have the manpower to enforce such a regulation.

The CNDF is also still unable to control advertising and promotional materials of of pharmaceutical companies for the same reason, lack of manpower. They agreed the Parke-Davis promotional materials we showed them were bad, especially the Chlorostrep ad and letter to doctors although I believe they were trying to say Chlorostrep is not nearly as potent as Chloromycetin since only 20% is absorbed . (However, the irreversible fatal aplastic anemia is not dose-related and can be triggered by very small doses as well as large doses.) They said the pharmaceutical companies just put out such promotional materials without CNDF's knowledge and they do not have the manpower to monitor it.

The CNDF officials also said that the Vademecum Daimon, comparable in Spain to our Physicians Desk Reference , widely used by physicians and put out by the pharmaceutical companies, isn't at all like our PDR nor up to it at all. But they said no other country has anything like the quality of the United States PDR and asked so how could Spain be expected to have something comparable? The gross inadequacy in warnings and use instructions of the product information in the Vademecum Daimon has been fully documented by a Spanish doctor.

They flatly stated that they do require all other companies to have the same warnings and use restrictions on all forms of their product as are on the original medicine that was changed, such as Parke-Davis's Chloromycetin. In the past, at a least, we are not sure this was so as there is quite a variation in the chloramphenicol labels of other Spanish companies. At least checking our labels, we are sure it was not and is not required verbatim as in the U.S. labels for chloramphenicol products but apparently they do believe in the principle. Whether it is adhered to and they can enforce it is another question which we did not ask.

Dr. Martinez Arroyo and Dr. Ferrandiz were very cordial and friendly, interested in any information we had as well as freely answering our questions even though the manner in which their health regulatory agency in the past handled the labeling of medicines by the pharmaceutical companies could have been embarrassing. They were so happy and hopeful of the change in the fortunes of their agency that they looked confidently toward a better future in this respect in their country. This optimism, though, was not shared by the physicians that we talked to earlier who felt that however good the new men are, that they will not be able to buck the powerful monied interests in the end. They did say, though, that there is some hope if a rumor that they had heard is true; that is, that the larger pharmaceutical companies in Spain were beginning to demand stricter labels (I presume Parke-Davis would be one of them) and that they had hopes this may have a good effect even though they felt the reason for the demand was to drive the smaller competitors out of business.

17. Centra Nacional de Farmacobiologia (CNDF('s new statements on chloramphenicol used as a basis for new labeling of chloramphenicol products of Parke-Davis and other companies in Spain.

Requested from:
Centro National De Farmacobiologia
(Control of Medicines) (their basis for labeling chloramphenicol medicines)
Madrid, Spain
Sep. 27, 1973

CHLORAMPHENICOL

Specific indications

1°. Acute infections caused by Salmonella Typhy (it is not indicated for treatment of the bearers).

2°. Acute infections caused by diverse salmonellas, H influenzae (specifically in meningitis infections), Ricketsias of the limphogranuloma-psittacosis group, Gram negative bacteria causing meningitis or bacteriemia and, finally, other organisms (sensitive) or resistant to all the rest of the anti-microbial agents.

Dosification: To the proper indication of the specialty, the following paragraph should be added:

"The daily dose for adults should not be over two grams, neither should be administered for more than ten days".

Secondary Effects:

After high dose and long treatments, chloramphenicol can give way to leukopenic, granulocitosis and anaemia, therefore it is very opportune to have hematic controls made during treatment.

In some cases it can also provoke neurological reactions of intolerance or hyperergias.

Counterindications:

Renal insufficiency and women in the first three months of gestation.

For newborns and premature babies doses over 25 mg/15 mg/kg/day are absolutely counter-indicated (respectively). The administration should be made via intramuscular and in one single dose.

CAUTION:

Its use should be reserved exclusively for the above mentioned indications.

See second statement - p.3

Acquired from:
Centro National De Farmacobiologia
(Control of Medicines)
Madrid, Spain
Sep. 28, 1973

CLORANFENICOL

INDICACIONES ESPECIFICAS:

1º.- Infecciones agudas por Salmonella Typhy (no estando indicado para tratamiento de portadores).

2º.- Infecciones graves por diversas cepas de salmonellas, H influenzae (especificamente en infecciones meníngeas), Ricketsias del grupo linfogranuloma-psittacosis, bacterias Gram - negativas causantes de meningitis o bacteriemia y, finalmente otros organismos sensibles que sean resistentes a todos/ los demás agentes antimicrobianos.

DOSIFICACION: Se añadirá a la propia de la especialidad el siguiente párrafo:

"La dosis diaria en adultos, no debe sobrepasar los dos - gramos, ni prolongarse más de díez días."

EFECTOS SECUNDARIOS:

A dosis elevadas y tratamientos prolongados, el cloranfenicol puede dar lugar a leucopenia, granulocitosis y anemia por lo que es oportuno realizar controles hemàticos durante el tratamiento.

En algunos casos puede provocar reacciones neurológicas, - de intolerancia o hiperèrgicas.

CONTRAINDICACIONES:

Insuficiencia renal y mujeres gestantes durante el primer/ trimestre del embarazo.

En recién nacidos y prematuros están absolutamente contraindicadas dosis superiores a 25 mg.- 15 mg./Kg. día, respectivamente. La administración será por vía intramuscular y en una sola dosis.

ADVERTENCIA:

Debe reservarse su uso exclusivamente para las indicaciones especificas reseñadas.

CHLORAMPHENICOL

The laboratory must justify the use of Chloramphenicol in this specialty since this is a useful but dangerous antibiotic, due to the incidence and seriousness of its secondary effects. Therefore it should be reserved for serious infections, for germs sensitive to its action, when other less efficient agents are counter-indicated.

Its specific indications are:

1. Acute infections caused by salmonella typhi (it is not indicated for persons suspected of disease bearing)
2. Serious infections by different groups of salmonella, H. influenzae (specifically meningitis), Rickettsia, the group of limphogranuloma psittacosis, gram negative bacteria responsible for meningitis and bacteremia. Finally, against other sensitive organisms which are resistant to all the other antimicrobial agents.

It is counter-indicated for individuals with hyper-sensitivity history or toxic reaction to the same and should not be used in cases of minor infections, colds, flu , throat infections or as a prophylactic to avoid bacterial infections.

CLORANFENICOL

El Laboratorio debe justificar el empleo de Cloranfenicol en esta especialidad, ya que éste es un antibiótico útil, pero peligroso, debido a la incidencia y gravedad de sus efectos secundarios, por lo cual debe reservarse para infecciones graves, por gérmenes sensibles a su acción, cuando otros agentes menos peligrosos son ineficaces o están contraindicados.

Sus indicaciones específicas son:

1º - Infecciones agudas por salmonella typhy (no estando indicado para tratamiento de portadores).

2º - Infecciones graves por diversas cepas de salmonella, H. influenzae (específicamente en infecciones meníngeas), Rickettsia, grupo del linfogranuloma-psittacosis, bacterias gram-negativas causantes de meningitis y bacteremia y, finalmente, otros organismos sensibles que sean resistentes a todos los demás agentes antimicrobianos.

Está contraindicado en individuos con antecedentes de hipersensibilidad o reacción tóxica al mismo y no debe usarse en infecciones leves, resfriados, gripe, infecciones de garganta ni como profiláctico para evitar infecciones bacterianas.

CERTAIN WORLD HEALTH ASSEMBLY ACTIONS RELATED TO PRODUCTION AND USE OF DRUGS

I. Pharmaceutical advertising -
Resolution WHA 21.41 (1968). Pg. 144 - Handbook of Resolutions and Decision - Ethical and Scientific Criteria for Pharmaceutical Advertising.

II. "Principles of Pharmaceutical Quality Control" and "Good Practices in the Manufacture and Quality Control of Drugs (Technical Reports Series No. 418 and WHO Official Record No. 176 Annex 12, part 1)
Resolutions WHA 22.50 (1969), WHA 23.45 (1970), WHA 24.56 (1971)
Handbook of Resolutions and Decisions: pgs. 133 and 134
Also WHA 28.65 (1975) in Technical Report Series 467.

III. Evaluation of the safety and efficacy of drugs -
Requests Member States to communicate immediately to WHO: a) any decision to prohibit or limit the availability of a drug already in use, b) any decision to refuse the approval of a new drug, and c) any approval for general use of a new drug when accompanied by restrictive provisions; when these decisions a), b) and c) are taken as a result of serious adverse reactions. They are also requested to include in the communication as far as possible the reasons for the action taken and the non-proprietary and other names, and the chemical formula or the definition.
Resolution WHA 16.36 (1963) - Handbook Resolutions and Decision, pg. 139
See also Res. WHA 17.39 (1964) - Handbook Resolutions and Decision, pg. 140

IV. "Monitoring of Adverse Effects of Drugs"
Resolutions: WHA 18.42 (1965), WHA 23.13 (1970). Handbook of Resolutions and Decisions - pgs. 140 and 141.
Technical Reports Series No. 498 - Role of national centres in international drug monitoring.

V. Study on: a) the feasibility of an international system providing data on the scientific basis and the conditions of registration and withdrawal of individual drugs; b) practicable minimum requirements and on other efforts to develop a comprehensive approach to ensuring the quality, safety and efficacy of drugs, including the feasibility of implementing Article 21 (d) and (e) of the WHO Constitution.
Resolutions: WHA 25.61 (1972), Handbook of Resolutions and Decisions pg. 143; and WHA 26.30 and WHA 26.31. WHO Official Records No. 209 pgs. 14 and 15 and No. 210 pgs. 294 to 307.

WHO Constitution

Article 21 - The Health Assembly shall have authority to adopt regulations concerning:

d) - standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce;

d) - advertising and labeling of biological, pharmaceutical and similar products moving in international commerce.

[From the Lancet, June 22, 1974, page 1281]

CHLORAMPHENICOL

SIR,—The indiscriminate use of chloramphenicol in many countries has been the subject of much concern and attention.[1-3] Ryrie et al.[4] warned particularly against the dangers of chloramphenicol being dispensed without prescription in Spain and reported the case of a woman who died of aplastic anæmia, some time after treating herself for a minor respiratory infection with a bottle of medicine containing chloramphenicol bought from a chemist's shop. This sad story clearly illustrates the danger of unrestricted dispensing, and even prescribing by the chemist's shop attendant, of chloramphenicol-containing drugs, but does not offer what could be called a quantitative view of the problem. In order to evaluate this, the following experiment was performed.

30 pharmacies in Barcelona were selected at random but in areas of different social class. A 32-year-old woman walked into each of these pharmacies and told the following story: "My 7-year-old boy has been ill with a fever of 38°C since yesterday. His throat is sore and there are white spots on his tonsils. What could I give him?" The attendants at 2 of these shops refused to indicate any treatment and suggested that she should call a physician. In the remaining 28 some type of remedy was prescribed, and sold. The most commonly dispensed remedies were:

(1) 11 cases: chloramphenicol, 100 mg.; plus sulphadiazine, 150 mg.; plus sulphamerazine, 150 mg.; plus aminopyrine, 75 mg.; plus camphocarboxylic acid, bismuth salt, 50 mg.

These ingredients were present in a brand of suppositories, to be used every twelve hours. In 6 cases, two days of treatment were recommended, while in 5 other cases four days of treatment were indicated. In 1 of these cases ampicillin (750 mg. daily for three days) was also given.

(2) 6 cases: chloramphenicol, 250 mg.; plus quinine sulphate, 120 mg.; plus phenylbutazone, 120 mg.; plus methampyrone, 250 mg.

This was also a fixed-dose drug combination presented as suppositories (to be used every twelve hours). In 4 cases a four-day course was prescribed and in the remaining 2, two days of treatment were indicated. In 1 of the last cases a further 700 mg. per day of aminopyrine was recommended; and in the other, 800 mg. of tetracycline phosphate complex daily, for two days, was also prescribed.

(3) 4 cases: chloramphenicol, 150 mg.; plus sulphadiazine, 100 mg.; plus sulphamerazine, 100 mg.; plus sulphamethazine, 100 mg.; plus camphocarboxylic acid, bismuth salt, 125 mg.; plus aminopyrine, 150 mg.; plus dexamethasone, 0·2 mg.

These were the ingredients of a brand of suppositories dispensed to be taken every twelve hours for two days. In 1 of these cases 750 mg. per day of an oral preparation of phenethicillin was recommended simultaneously. In another, extra tablets of aminopyrine were also sold.

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1. *Lancet*, 1972, ii, 1298.
2. Dunne, M., Herheimer, A., Newman, M., Ridley, H. *ibid.*, 1973, ii, 781.
3. Verwilghen, R. L., Verstraete, M. *ibid.* p. 1217.
4. Ryrie, D. R., Fletcher, J., Langman, M. J. S., Daniels, H. E. *ibid.* 1973, i, 150.

(4) Suppositories containing different mixtures of chloramphenicol plus sulphonamides, tetracycline, and aminopyrine, as well as other components, were sold in 4 other cases, the suggested duration of treatment ranging from one and a half to three days. In one of these cases oral ampicillin, 750 mg. per day, was also prescribed for three and a half days.

(5) In 1 of the remaining 3 cases oral ampicillin was dispensed (750 mg. per day for three and a half days) and in the other 2 tetracycline phosphate complex was given to be taken orally at a dose of 375 mg. daily for two days.

The results of these experiments hardly need any comment. However, we cannot refrain from specifically mentioning the irrationality of the mixtures dispensed, and the presence in them of potentially dangerous drugs, such as chloramphenicol, aminopyrine, and phenylbutazone, to mention only a few. Moreover, the insufficiency of the doses and the short duration of the treatment, as well as the inadequacy of the route of administration, could bring only little therapeutic benefit, while the danger of serious side-effects remained. Finally, the fact that all these remedies were unrestrictedly sold, while almost two-thirds of them carried a "dispensed by prescription" sign, deserves consideration.

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[From the Washington Post Travel Section, March 13, 1977]

Rx for Tourists: Beware the Foreign Prescription Drug

By Milton Silverman

TRAVELERS, especially those heading for Latin America, Southern Europe, Asia, and Africa, have long been accustomed to getting admonitions like these:

•Don't drink the water.

•Don't eat uncooked vegetables.

•Avoid ice cream, whipped cream and other products that may have been made from unpasteurized milk.

Now a new and perhaps far more important warning should be added:

•Beware the physician who prescribes drugs, and also the pharmacist who may both prescribe and dispense them, who may be unaware of the limited value of these products and of their potentially harmful or fatal side-effects.

Last year, after a long, in-depth study in Mexico, Central America and South America, it was disclosed that some of these health professionals are giving out a potentially deadly antibiotic to patients suffering from such trivial infections as tonsillitis and laryngitis.

Some have treated depression with a combination of drugs that can interact to cause death.

Some are keeping patients on steroid hormones for such prolonged periods that some have suffered from bone-softening, pressure fractures of the vertebrae, psychotic changes and flare-ups—sometimes fatal—of latent tuberculosis and other infections.

Some have administered excessive dosages of potent anti-arthritis drugs, resulting in serious or lethal damage to the blood-forming tissues.

These and similar prescribing blunders, now thoroughly documented by Latin American hematologists, pathologists and other experts, do not mean that Latin American physicians and pharmacists are poorly trained, poorly motivated or unable or unwilling to keep up-to-date. Some of the health care rendered in the Latin American countries is fully comparable to the best medicine practiced in Washington, Boston, London or Stockholm. On the other hand, some medical care rendered in Latin America is as poor as the worst practiced in the United States.

Instead, this misuse of drugs in Latin America— and also in such other countries as Spain, Egypt, India and Taiwan —appears to be a reflection of the astounding drug promotion and drug labeling disseminated to physicians and pharmacists by much of the pharmaceutical industry. In this "educational" material furnished by many drug companies, the efficacy or usefulness of the drugs is too often grossly exaggerated, and the possible hazards are minimized, glossed over or totally omitted.

Or, the promotion may essentially warn the physician, "This drug may produce nose stuffiness," while failing to mention, "This drug may kill your patient."

In our investigation we compared the promotional material furnished to physicians in the United States and Latin America on 26 well-known, widely used prescription drug products marketed under 40 different brand names by 23 global pharmaceutical firms. Some of these companies were based in the United States. Others had their headquarters in Switzerland, France or West Germany.

In the United States, where drug promotion and labeling is under the strict control of the U.S. Food and Drug Administration (FDA), each company is required to limit its claims of usefulness to those that can be supported by substantial scientific evidence. All potential hazards must be clearly disclosed, and occasionally FDA requires the warnings to be printed in extra large type.

In the Latin American countries, however, a different situation prevails, and the companies generally say whatever they want to say.

One of the most notable cases has involved the antibiotic chloramphenicol, marketed in many countries by many different companies.

In the United States, it is described as indicated only for such life-threatening infections as typhoid fever, Rocky Mountain spotted fever, a rare form of meningitis in children and a few other conditions in which it is considered clearly the drug of choice. Physicians in this country are warned that it may cause infrequent but serious side-effects, including a blood disorder known as aplastic anemia that, in some cases, carries a mortality rate of 30 to 60 per cent. The drug, the labels say, should not be used for trivial infections.

But in Latin America, some companies have recommended chloramphenicol for laryngitis, tracheobronchitis, pneumonia, gonorrhea, syphilis, abscesses and other diseases in which other and safer drugs can be used. In those countries, the warnings and contraindications are minimal or entirely omitted.

When this situation was called to the attention of the drug companies concerned, the responses included such explanations as these:

"Latin American doctors don't need any warnings. They already are aware of the dangers"—an explanation that infuriates medical educators and other experts.

"Things are different in Latin America"—a view that seems to suggest that drugs are far more effective and safer south of the Rio Grande.

"What's involved here is an honest difference of opinion—we feel we have enough evidence to show that our drug is acceptably safe, but we can't convince the Food and Drug Administration."

This last explanation would probably be more palatable if the company said one thing in the United States, where its statements are under the heavy hand of FDA, and something different in all of Latin America, where the rules are less rigid.

"But," said one Colombian health official, "when we find the company tells one story here in Bogota, another in Quito, another in Brasilia and still another in Mexico City, that is difficult to comprehend."

Finally, drug companies have put up as their major defense, "We're not breaking any laws." They claim that their foreign subsidiaries or affiliates are managed by nationals of the country who know the laws and regulations, and who obey them scrupulously.

Our survey, including an examination of Latin American drug laws, showed that this defense was valid in some countries. The companies were not violating any drug promotion laws because no such laws were in existence. In others, the situation was unclear, with the laws difficult to analyze. But in at least four countries—Colombia, Honduras, El Salvador and Panama—laws controlling drug promotion are on the books, and companies were breaking those laws.

So far as we can determine, none of these practices can be controlled by U.S. laws.

Complicating the situation are other factors:

Most Latin American physicians are employed by the government and paid relatively low salaries. In contrast, the company detail men—the "*visitadores*" who promote their products to physicians—are employees of private industry, usually paid at least partly by commissions, and not inclined to knock their own drugs. Many of these detail men have had only a high school education.

Although many drugs legally require a prescription written by a physician, this requirement—except for morphine and its relatives, and for some tranquilizers— is frequently ignored. In most pharmacies, a patient can get a prescription product merely by asking for it. Or the patient can describe his symptoms to the pharmacist, and the pharmacist will then diagnose, prescribe and dispense.

If a patient is injured by a prescription drug, the company, the physician and the pharmacist are generally safe from retribution. There are essentially no effective medical malpractice or product liability laws in most of the countries.

As an example of what can happen in this complex situation, we observed the case of a woman—thin, nervous, jittery—who went into a large pharmacy in Costa Rica and asked by name for a potent tranquilizer. The clerk said he had something far better, and sold her a supply of what we recognized as a powerful but dangerous thyroid drug. It may have been the appropriate drug for her. But what made the event memorable is that we were unable to tell whether the clerk—who acted without consulting any of his colleagues—was aged 14, 13, or 12.

Since these findings were published in May of 1976, and simultaneously presented in testimony before the U.S. Senate Subcommittee on Monopoly, there have been signs that the situation may be corrected more swiftly than had been anticipated:

•The findings were widely reported throughout Latin America by newspapers, radio and television.

•In a number of global drug companies, some officials—especially those concerned with research and medical affairs—are urging their firms to follow the same promotional policies they use in the United States in all their foreign promotion.

•The United States delegation to the International Federation of Pharmaceutical Manufacturers has called for standardized drug promotion, worldwide, with full disclosure of hazards.

•At least one major drug company in this country has already changed its promotion in Central America, limiting the claims for its products and disclosing their dangers.

Until all companies follow this lead, however, many physicians and pharmacists in many countries may continue to be uninformed or misinformed, and travelers should remain forewarned.

Milton Silverman, Ph.D., is a pharmacologist and biochemist, lecturer in pharmacology, School of Pharmacy, and senior faculty member, Health Policy Program, in the School of Medicine at the University of California, San Francisco. He is the author of "The Drugging of the Americas."

Prescription Drug Checklist

A few tips to world travelers on avoiding dangerous use of prescription drugs:

Remember the drugs to which you are—or think you may be—allergic. Before you start your travels, consult your own physician on which drugs—especially those for the control of pain and diarrhea—are both effective and relatively safe. Note that many painkillers and antidiarrhea agents popularly prescribed and used in other countries are considered ineffective or unsafe and accordingly are not permitted on the United States market.

Insist that a physician prescribing a drug for you abroad must tell you the possible serious side-effects, and which warning symptoms to keep in mind. Use caution in taking a prescription drug recommended by anyone other than a physician who prescribes it specifically for you.

If you are on long-term medication, take along an adequate supply. If you may need to replenish your supply while you are out of the country, have your own physician or pharmacist give you the generic (or internationally accepted) name of the drug. In many foreign countries, the product may be marketed under a different brand name.

If a physician plans to prescribe a drug for you, tell him what other drugs—prescription or over-the-counter—you are also taking. Drug-drug interactions can be lethal.

If anyone—physician, pharmacist or fellow tourist—tells you that a particular drug is perfectly safe, don't believe him. With few if any exceptions, any drug that is effective can also be harmful and, in some conditions, can be fatal.

—*Milton Silverman*

[From the Washington Post, March 20, 1977]

DRUG FIRMS SOFTEN SALES PITCHES TO CENTRAL AMERICANS

(BY MORTON MINTZ)

Major multinational pharmaceutical firms doing business in Central America have begun to tone down promotions of potent drugs to physicians by limiting claims of benefits while making fuller disclosure of risks.

This finding was made by Dr. Milton Silverman, a University of California drug specialist who compared what 15 global companies—American, Swiss and French—were telling Central American doctors in 1973 with what they began to tell them in 1976.

Silverman, who reviewed 26 widely used drugs, gave this summary of his findings:

• For nine medicines, the manufacturers narrowed claims of effectiveness and strengthened the warnings to make them comparable to those they provide physicians in the United States, where the Food and Drug Administration requires proof of safety and effectiveness.

• For two products, the producers were already making "reasonably full disclosure in 1973 and have continued to do so."

• For 11 drugs, the companies "are continuing to exaggerate the clinical values of the drugs and to minimize, gloss over, or totally ignore the potentially serious or fatal side effects."

• For four drugs, the manufacturers "elected to solve the problem by the expedient of not publishing anything in 1976 about them."

Probably the most dramatic change involved Chloromycetin, the Parke-Davis brand of an antibiotic, chloramphenicol, that causes a fatal blood disease in some users.

In the United States, the FDA has long required the Detroit firm to say in the official prescribing instructions and advertisements that chloramphenicol should not be used in "trivial infections," but should be restricted to a few serious or life-threatening diseases such as typhoid fever.

The labeling also warns of the link to the blood disease.

In Latin America in 1973, Silverman said, Parke-Davis was contradicting the advice it was giving in the United States by recommending Chloromycetin for disorders including tonsillitis, pharyngitis, eye and ear infections, abscesses and pneumonia. It did not disclose potential adverse reactions including the blood disease, nor give, the medical conditions in which the drug should not be used.

By 1976, however, Parke-Davis was telling Central American physicians virtually the same thing it was telling physicians here, Silverman said.

He based his findings on the 1973 and 1976 entries in the Central American Spanish-language edition of the "Dictionary of Pharmaceutical Specialities."

This is a widely used reference volume that carries entries exactly as companies want them and it is distributed annually to every doctor in Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama, along with the Dominican Republic.

The 1976 edition was published Sept. 30, four months after the University of California Press published Silverman's book, "The Drugging of the Americas," and after the author testified before the Senate Select Small Business Monopoly Subcommittee.

The book and testimony were based on a first-hand survey by Silverman and two associates, who compared the labeling of 40 drugs provided by 23 international companies in the United States with the labeling they provided on the same products in 11 Latin American countries.

Although some companies defended the legality of overstating benefits and understating risks outside of the United States, Silverman testified that they were violating laws in four countries—Honduras, Panama, El Salvador and Colombia—that required full disclosure of hazards to physicians.

News reports on the Senate hearing were widely published in Latin America, Silverman said.

At the time, C. Joseph Stetler, president of the Pharmaceutical Manufacturers Association in Washington, acknowledged "the importance of the questions raised" in the hearing and said he intended to have them discussed by the International Federation of Pharmaceutical Manufacturers.

Three weeks later, Stetler went before a meeting of the federation in London with an unprecedented proposal: to adopt a resolution calling upon the world's drug companies to adhere to standardized drug labeling and to make full disclosure of hazards.

Stetler said recently that he raised the issue in part because of the Senate hearing and, in an apparent reference to the publicity, "in part because of recurring concern expressed in various other quarters."

The federation rejected Stetler's proposal, asking him instead to prepare a policy statement. As adopted by the federation at a meeting in November, the resolution said:

- That labeling and entries in prescribing guides for a prescription drug "should be consistent with the body of scientific and medical evidence pertaining to that product, taking into account good medical practice and the requirements of each government's regulatory authorities."
- That "particular care should be taken that essential information as to medical products' safety, contraindications and side effects is appropriately communicated."
- That each of the more than 40 member associations "encourage compliance among its member companies with this proposal."

Silverman commented that the federation "unhappily . . . did not propose any method to implement the move." He said that a body such as the World Health Organization could "set up guidelines and maintain surveillance." He added:

"It remains to be seen whether the changes instituted by some global drug companies in Central America will be applied to all their products throughout the world, and whether their lead will be followed by other drug firms."

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1326 THIRD AVENUE
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February 28, 1977

Senator Gaylord Nelson
Chairman, U.S.Senate
Small Business Committee
424 Russell Senate Office Building
Washington, D.C. 20510

Dear Senator Nelson:

I am sure you will recall that, with a number of my colleagues, I was pleased to respond to your invitation and to testify before the Subcommittee on Monopoly in May of 1976 on the manner in which global pharmaceutical companies were labeling and promoting their products to physicians in Latin America.

As based on what many of these companies were stating to Latin American physicians in 1973 editions of standard reference volumes, this was the situation:

1. In most instances, the Latin American claims for the values of these products were grossly exaggerated.

2. In most instances, the warnings, contraindications, and potential serious or lethal adverse reactions were minimized, glossed over, or totally ignored.

3. Regardless of the protestations of the companies that they were fulfilling their ethical and moral responsibilities, and were not violating any laws in the Latin American countries involved, most were actually breaking national laws in at least four of those countries.

I am now glad to respond to your request to bring this information up to date.

Within the first three weeks after your hearings, the findings of our study were extensively reported in major newspapers, radio, and television throughout Latin America. Various Latin American embassies in Washington, D.C., requested additional information, which we were happy to furnish. On June 16, in London, the United States delegation to the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) urged standardized labeling and promotion of drug products, worldwide, with disclosure of hazards.

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During the summer of 1976, we were pleased to reply to requests for additional information from numerous medical, pharmacy, economic, and legal organizations and research centers and individuals in Mexico, Central America, South America, the United Kingdom, France, Belgium, Canada, and the United States. Similar requests were received from individual pharmaceutical firms, and representatives of some of these companies visited us in San Francisco to consult on aspects of the problem.

On November 11, at its meeting in Bermuda, the council of the IFPMA adopted a resolution--formally introduced by the United States delegation--calling upon every drug company to see that labeling "should be consistent with the body of scientific and medical evidence pertaining to that product," and that "particular care should be taken that essential information as to medical products' safety, contraindications and side effects is appropriately communicated."

It is my understanding that this resolution has been informally brought to the attention of the World Health Organization.

Perhaps most significant, however, are steps taken even earlier by a number of multinational drug companies. It has recently been possible for us to study the 1976 issue (published in September 1976) of the Central American edition of the Diccionario de Especialidades Farmeuticas, and compare the promotional statements made to physicians in 1973 (when we began our research) with those made in 1976. For 26 products, marketed by 15 global companies--United States, Swiss, and French--these developments were evident:

--For 9 products, the companies have elected to tone down their claims and present warnings comparable to those they give to physicians in the United States.

- For 2 products, the companies were already making reasonably full disclosure in 1973 and have continued to do so.

- For 11 other products, the companies--in some cases in violation of Central American laws--are continuing to exaggerate the clinical values of the drugs and to minimize, gloss over, or totally ignore the potentially serious or fatal side effects.

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--For 4 products, the companies have elected to solve the problem by the expedient of not publishing any promotional material about the drugs in the 1976 edition.

Perhaps the most striking change involves Parke-Davis' chloramphenicol, an important antibiotic marketed under the name of Chloromycetin. In the United States, the company has told physicians that its use should be restricted to a limited number of serious or life-threatening diseases, such as typhoid fever, in which practically no other and safer product is as effective. It should not be used in "trivial infections." Physicians are warned that its demonstrated hazards include the possibility of producing a highly lethal aplastic anemia or other blood dyscrasia.

In the Central American countries and elsewhere in Latin America, however, the description of Chloromycetin in 1973 included recommendations for its use in tonsilitis, pharyngitis, eye and ear infections, pneumonia, and abscesses. In the 1973 Central American reference volume, not one contraindication, warning, or potential adverse reaction was disclosed.

In the 1976 Central American edition, however, Parke-Davis said Chloromycetin should be used only in serious conditions and never for "trivial infections." There is virtually complete disclosure of contraindications and dangers, including the possible appearance of aplastic anemia.

Although much remains to be accomplished, I trust you will share in our gratification that some changes have come about. It is conceivable that some lives will be saved.

I trust also that you are aware that my colleagues and I are grateful to you personally and to other members of your Subcommittee for the constant and courageous support you have given us over the past years, and to Mr.Benjamin Gordon for his unfailing assistance. Without such help, much of our work would have been impossible.

Cordially yours,

Milton Silverman, Ph.D.