DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(5), 1059-1072 (1985)

# WORLDWIDE QUALITY - IS IT UNIFORMLY CONTROLLED?

PRESENTED BY: DONALD SPIEGEL
DIRECTOR OF QUALITY CONTROL
WHITEHALL INTERNATIONAL, INC.

NATIONAL EXHIBITION AND CONFERENCE FOR THE PHARMACEUTICAL INDUSTRY
RxPO
ESSEX HOUSE/NEW YORK COLISEUM
JUNE 20, 1984

## ABSTRACT

WORLDWIDE QUALITY - IS IT UNIFORMLY CONTROLLED

Multiple controls during the manufacture of pharmaceutical products are considered essential for the achievement of consistent high quality in such products. The problem normally associated with manufacturing high quality products are multiplied in the international marketplace. Global scale problems associated with regional jurisdictions and varied control standards will be discussed in detail.

## INTERNATIONAL QUALITY CONTROL

GOOD MORNING. NOW THAT WE HAVE HEARD OF SPECIFIC REGULATORY PROBLEMS WORLDWIDE, I'D LIKE TO BLEND THESE CONCEPTS WITH QUALITY CONTROL.

IT IS ERRONEOUS TO BELIEVE THAT JUST THE ANALYSIS OF THE FINISHED PRODUCT, IS SUFFICIENT TO ENSURE COMPLETE PRODUCT QUALITY. A SERIES OF CONTROLS, DURING THE ENTIRE MANUFACTURING PROCESS, IS ALSO NECESSARY TO MAINTAIN ADEQUATE CONTROL.

CONTROL OF PHARMACEUTICAL MATERIALS IS NOT NEW. IT HAS BEEN DONE FOR MANY YEARS. HISTORICALLY, LOCAL PHARMACOPOEIAS GREW OUT OF





0363-9045/85/1105-1059$3.50/0

CATALOGS, WITH ONE OF THE EARLIEST BEING THE BRITISH PHARMACOPOEIA OF 1864. TODAY, WE HAVE COME A VERY LONG WAY IN LAYING DOWN STANDARDS FOR PURITY AND STRENGTH OF PHARMACEUTICAL INGREDIENTS IN ORDER TO PREVENT THEIR ADULTERATION AND MISDIRECTION.

WHEN AN INDIVIDUAL BUYS A RAW MATERIAL OR FINISHED PRODUCT IN LONDON, TOKYO OR NEW YORK, AND IT HAS THE IDENTIFYING INITIALS - USP - NF - BP - IP, AFTER IT, ONE KNOWS THAT THE MATERIAL HAS MET CERTAIN REQUIREMENTS FOR PURITY AND STRENGTH ACCORDING TO A RECOGNIZED PHARMACOPOEIA.

MODERN PHARMACEUTICALS ARE NOW SUCH POTENT PRODUCTS THAT IT IS GENERALLY AGREED THAT THE SOLE RESPONSIBILITY FOR THEIR SAFE PRODUCTION CAN NO LONGER BE LEFT ENTIRELY TO THE MANUFACTURER.

WORLDWIDE, VARIOUS GOVERNMENTAL REGULATORY AGENCIES, HAVE INFLUENCE OVER THE MANUFACTURE AND CONTROL OF PHARMACEUTICAL PRODUCTS. IN THE UNITED STATES, GOOD MANUFACTURING PRACTICES ARE ENFORCED BY LAW, TO MAKE SURE THAT THE PHARMACEUTICAL PRODUCTS THAT ARE PLACED INTO INDUSTRIAL COMMERCE CHANNELS ARE SAFE AND EFFECTIVE. THIS REGULATORY AGENCY HAS A SERIES OF INSPECTORS, WHO NOT ONLY CONDUCT PERIODIC SAMPLING AND MARKETPLACE SPOT CHECKING, BUT MORE IMPORTANTLY, EVALUATE OPERATIONS IN ORDER TO SEE THAT PRACTICES AND CONTROL SYSTEMS NOT ONLY EXIST, BUT ARE USED, ACCORDING TO SPECIFIC WRITTEN PROGRAMS.

INTERNATIONALLY, THERE ARE REGULATORY PRACTICES, RECOMMENDED FOR THE MANUFACTURE AND CONTROL OF PHARMACEUTICAL PRODUCTS, ISSUED BY THE WORLD HEALTH ORGANIZATION. THESE REGULATIONS ARE BASED UPON REQUESTS FROM DEVELOPING COUNTRIES SEEKING PROTECTION FROM THE INFLUX OF SECOND RATE PRODUCTS.

THE DEVELOPING COUNTRIES HAVE ALWAYS BEEN FEARFUL THAT THE PRODUCING COUNTRIES MAY "DUMP" SUBSTANDARD DRUG PRODUCTS CONTAINING ABOVE LIMIT DEGRADATION MATERIALS AND IMPURITIES, OR HAVE INCOMPLETE LABELING TEXTS, WHERE IMPORTANT WARNING STATEMENTS HAVE BEEN OMITTED. APART FROM THIS, THESE AREAS MAY NOT HAVE ADEQUATE FACILITIES FOR THE

PROPER LABORATORY CHECKING OF THESE PRODUCTS. THIS PRESENTS A PROBLEM OF A DIFFERENT NATURE.

IN 1975, THE WORLD HEALTH ORGANIZATION ADOPTED "GOOD PRACTICES IN THE MANUFACTURE AND QUALITY CONTROL OF DRUGS", RECOGNIZING THE FACT THAT CONTROLS DIFFER FROM COUNTRY TO COUNTRY. THIS IS NOT REALLY SURPRISING, WHEN ONE CONSIDERS THE VARIOUS CONDITIONS WHICH EXIST, AS PROMULGATED BY LOCAL DRUG LEGISLATIONS, IN DIFFERENT PARTS OF THE WORLD.

ALONG WITH THIS, THE WORLD HEALTH ORGANIZATION ADOPTED A "CERTIFICATION SCHEME" WHICH PLACED THE RESPONSIBILITY ON THE MANUFACTURER FOR THE QUALITY OF THE DURG PRODUCT THAT HE EXPORTS. ACCORDINGLY, THERE HAS TO BE INTERNATIONAL UNDERSTANDING AND AGREEMENT, WHEREBY AN IMPORTING COUNTRY CAN ACCEPT, WITH ASSURANCE, THAT ESTABLISHED PHARMACEUTICAL QUALITY CONTROL STANDARDS ARE ENFORCED BY THE EXPORTING COUNTRY FOR THE PRODUCT THEY RECEIVE FOR LOCAL SALE.

APPROXIMATELY TEN MONTHS AGO, THE INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ABBREVIATED AS IFPMA, MADE PROPOSALS TO MODIFY THE CURRENT W.H.O. CERTIFICATION SCHEME.

THE CURRENT W.H.O. CERTIFICATE PROVIDES ASSURANCE, THAT THE EXPORTED PRODUCT IS MANUFACTURED UNDER SUITABLE CONDITIONS IN ACCORDANCE WITH GMP, AND THAT THE MANUFACTURING PREMISES ARE SUBJECT TO INSPECTION AT SUITABLE INTERVALS. IT ALSO RECORDS WHETHER OR NOT THE PRODUCT IS AUTHORIZED TO BE PLACED ON THE MARKET IN THE COUNTRY OF ORIGIN.

THESE PROPOSALS ARE AS FOLLOWS:

1) INFORMATION SHOULD BE INCLUDED WHICH DESCRIBES THE PRODUCT'S INDICATIONS AND DOSAGE WARNINGS, TAKING INTO ACCOUNT ESTABLISHED FACTORS OF SAFETY AND EFFICACY.

2) THE MANUFACTURING CERTIFICATE WOULD GIVE INFORMATION REGARDING THE SHELF LIFE AND THE SPECIFIC STORAGE CONDITIONS FOR WHICH THE SHELF LIFE IS VALID.

3) WHERE REQUIRED BY THE IMPORTING COUNTRY, EACH BATCH OF THE PRODUCT WOULD ALSO BE ACCOMPANIED BY A BATCH CERTIFICATE AS SPECIFIED IN THE "W.H.O. CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING INTERNATIONAL COMMERCE."

4) THE PROPOSED MANUFACTURER'S CERTIFICATE WOULD ALSO INCLUDE MEDICAL AND PRESCRIBING INFORMATION FOR THE PRODUCT AND ITS LABELLING.

ADDITIONALLY, RELEVANT BACKGROUND INFORMATION ON THE INDICATIONS, USES, PRECAUTIONS AND CONTRAINDICATIONS FOR THE PRODUCT WOULD HAVE TO BE INCLUDED.

THESE ARE VERY ENCOMPENSING PROPOSALS.

THIS SCHEME AND FUTURE AMENDMENTS TO IT SHOULD HARMONIZE THE REQUIREMENTS WHICH WOULD TAKE THE GUESSWORK OUT OF REGULATORY. IT MAY PLACE A BURDEN, HOWEVER, ON THE LESS DEVELOPED NATIONS BY POTENTIALLY SLOWING DOWN PROGRESS IN THESE AREAS, FROM THE STANDPOINT THAT THE CERTIFICATE MAY JUST BE USED FOR THE RECORD. THIS WOULD DIMINISH ITS POTENTIAL BENEFITS.

HOWEVER, THIS MODIFIED W.H.O. CERTIFICATION SCHEME, IF ASSIMILATED INTO THE INDIVIDUAL NATIONAL REGISTRATION REQUIREMENTS, WILL HELP TO SPEED UP THE REGULATORY PROCESS. THEN, COUNTRIES WILL NOT HAVE TO DIGEST DOCUMENTATION ON THEIR OWN, BECAUSE A SUBMISSION, SUCH AS THIS, WILL HAVE THE W.H.O.'S SEAL OF APPROVAL.

WITHOUT THE W.H.O. CERTIFICATE, A THIRD WORLD COUNTRY, IF GIVEN ADDITIONAL INFORMATION NOT REQUIRED THROUGH THEIR LAWS, WOULD FEEL COMPELLED TO DIGEST, DISECT AND COMMENT ON THE TECHNICAL DATA RECEIVED. GIVEN THE REGULATORY EXPERTISE NOW DISPLAYED BY MANY THIRD WORLD MINISTRIES, THIS IN EFFECT MAY BE DETRIMENTAL TO ENSURING AND SAFEGUARDING THE HEALTH OF THEIR CONSTITUENTS. IN THE END, A HARMONIZATION OF REGISTRATION REQUIREMENTS WILL MAKE OUR JOB AND THEIRS EASIER.

ALL IN ALL, THE CURRENT AND PROPOSED CERTIFICATION SCHEMES ARE A GOOD STEP FORWARD IN PROVIDING INFORMATION WHICH MORE FULLY CHAR-

ACTERIZES AND DESCRIBES THE PRODUCT WHICH THE EXPORTING COUNTRY IS ATTEMPTING TO REGISTER FOR SALE. I DO NOT FORESEE THAT THIS ADDITIONAL INFORMATION WOULD COMPEL THE RESPECTIVE MINISTRIES TO CHANGE THE STATUS FROM "OTC" TO "PRESCRIPTION" FOR SOME OF THE PRODUCTS, AS THE REAL BENEFIT OF SUCH A PROGRAM WOULD ONLY BE DILUTED BY CONFUSION DUE TO THE ADDITIONAL QUESTIONS THAT MIGHT ARISE FROM ANY GOVERNMENTAL RESTRICTIONS IMPOSED BY THE IMPORTING COUNTRY.

WHILE THE EMPHASIS IN THE PAST HAS BEEN ON MORE ETHICALLY-ORIENTED PHARMACEUTICALS OVERSEAS, INCREASING ATTENTION HAS BEEN GIVEN TO OTC PREPARATIONS, AS IS THE CASE IN THE UNITED STATES. THEREFORE, THERE IS A NEED FOR A UNIFORM STANDARD OF QUALITY FOR DRUG PRODUCTS FORMULATED AND PACKAGED BY U.S. PHARMACEUTICAL MANUFACTURERS WHEREVER THEY ARE PRODUCED WITHIN A COMPANY'S ORGANIZATION. CONSIDERATION TOO, MUST BE GIVEN TO SUCH FACTORS AS LOSS OF SALES, WHICH COULD RESULT FROM THE UNAVAILABILITY OF MERCHANDISE DUE TO MANUFACTURED PRODUCTS OF SUBSTANDARD QUALITY. IT IS STILL THE QUALITY PRODUCT ITSELF THAT ACCOUNTS FOR REPEAT SALES. OCCASIONALLY, LOCAL PROBLEMS WILL ARISE AND WILL HAVE TO BE TREATED ON AN INDIVIDUAL BASIS, BUT THE EXERCISE OF SOUND JUDGMENT TO AVOID COMPROMISING THE COMPANY'S QUALITY CONTROL OBJECTIVES OR POLICIES, SHOULD BE THE GOAL.

INTERNATIONALLY, THE DEVELOPING COUNTRIES IN ASIA HAVE LONG REALIZED THE IMPORTANCE OF ENSURING CONTROL OF THE QUALITY OF PHARMACEUTICAL PRODUCTS, NOT ONLY AS A FUNDAMENTAL PREREQUISITE FOR EFFICIENT MEDICAL CARE, BUT ALSO AS A MEANS TO PROTECT THE PUBLIC FROM THE DANGER OF DEFECTIVE DRUGS.

THE PHILIPPINE GOOD, DRUG AND COSMETIC ACT, IMPLEMENTED DURING THE MIDDLE OF 1966, ESTABLISHED GMP'S AS RECOMMENDED BY THE WORLD HEALTH ORGANIZATION. ENFORCEMENT PROCEDURES STARTED IN THE BEGINNING OF 1971, BUT INITIALLY ENCOUNTERED DIFFICULTIES WITH SMALL DRUG MANUFACTURERS DUE TO THE SKILL LEVELS LOCALLY AVAILABLE TO HANDLE MANUFACTURING OPERATIONS. THIS HAS BEEN IMPROVED SIGNIFICANTLY OVER THE YEARS.

THE MANUFACTURE AND DISTRIBUTION OF DURGS IN JAPAN IS COVERED BY CHAPTER IV OF THEIR PHARMACEUTICAL AFFAIRS LAW. LOCAL APPROVAL BY THEIR MINISTER OF HEALTH AND WELFARE IS REQUIRED FOR THE MANUFACTURE OF EVERY DRUG NOT RECOGNIZED IN THE JAPANESE PHARMACOPOEIA. CONTROL TESTING OF MATERIALS IS EXTREMELY THOROUGH AND INVOLVES A COMPREHENSIVE STATISTICAL EVALUATION, WHICH AT TIMES EXCEEDS THAT DESCRIBED IN MIL STD 105.

IN 1979, THE JAPANESE PARLIAMENTARY "DIET" AMENDED THEIR PHARMACEUTICAL AFFAIRS LAW, EMPOWERING THEIR MINISTRY OF HEALTH AND WELFARE TO ENFORCE PHARMACEUTICAL MANUFACTURING AND QUALITY CONTROL, BY ISSUING GOOD MANUFACTURING PRACTICE RULES AS MINISTERIAL ORDINANCES.

THE OPPOSITE PICTURE IS FOUND IN HONG KONG, WHERE THEY ONLY HAVE A "DANGEROUS DRUGS ORDINANCE ACT" - THE WHOLESALER NEED ONLY TO OBTAIN A "POISON LICENSE" FROM THE GOVERNMENT. THERE IS LITTLE REGULATION OVER THE IMPORTATION OF PHARMACEUTICAL PRODUCTS WITH THE EXCEPTION OF A FEW DANGEROUS "DRUGS", HYPNOTICS AND HALLUCINOGENS SUCH AS LSD. THERE IS A PRODUCT LICENSE PROCESS, HOWEVER, AND THE GOVERNMENT WILL ANALYZE A PRODUCT ONLY AFTER COMPLAINTS HAVE BEEN FILED.

SOUTH KOREAN REGULATIONS ARE MORE RESTRICTIVE. THE KOREAN LAW AUTHORIZES REGULAR GOVERNMENT INSPECTIONS OF MANUFACTURERS. THESE REGULATIONS ALSO REQUIRE LICENSED ESTABLISHMENTS TO COMPLY WITH GOVERNMENTAL STANDARDS FOR QUALITY CONTROL LABORATORY FACILITIES. THESE SOUTH KOREAN STANDARDS, KNOWN AS KGMP'S, ARE IN LINE WITH THE GUIDELINES DEVELOPED BY THE WORLD HEALTH ORGANIZATION.

THEIR NATIONAL INSTITUTE OF HEALTH, IN ACCORDANCE WITH THESE REGULATIONS, PRESCRIBES STATEMENTS OF IDENTITY, STRENGTH, QUALITY, PURITY AND SAFETY, WHICH GOVERNS HOW THE MATERIALS ARE TO BE ALLOWED FOR DISTRIBUTION WITHIN THE COUNTRY. THE KOREAN HEALTH AUTHORITIES COLLECT AND ANALYZE SAMPLES FROM THEIR LOCAL MARKETPLACE.

IN TAIWAN, PHARMACEUTICAL MANUFACTURING IS COVERED BY THE "LAW FOR THE CONTROL AND REGULATION ON MEDICINES AND DRUGGISTS" AND PROVIDES FOR THE CREATION OF A CENTRAL REGULATORY AGENCY, WHICH IS

CHARGED WITH THE RESPONSIBILITY OF IMPLEMENTING SUITABLE PROCEDURES TO CONTROL THE MANUFACTURE, SALE AND DISTRIBUTION OF PHARMACEUTICAL PRODUCTS. THE TAIWANESE CENTRAL HEALTH AUTHORITY, MANDATED SPECIFIC PROVISIONS WHICH AUTHORIZE PROVINCIAL AND MUNICIPAL HEALTH AUTHORITIES TO CONDUCT PERIODIC INSPECTIONS OF ESTABLISHMENTS USED FOR THE MANUFACTURING OF DRUG PRODUCTS, INCLUDING QUALITY CONTROL VERIFICATION PROCEDURES.

IN AUSTRALIA, THE NATIONAL BIOLOGICAL STANDARDS LABORATORY OF THE COMMONWEALTH DEPARTMENT OF HEALTH, ISSUED A CODE OF GOOD MANUFACTURING PRACTICES FOR THERAPEUTIC GOODS MODELED ON THOSE PUBLISHED BY THE WORLD HEALTH ORGANIZATION.

THE NEW ZEALAND DEPARTMENT OF HEALTH PUBLISHED A "CODE OF GOOD PRACTICE FOR MANUFACTURE AND DISTRIBUTION OF MEDICINES" BASED UPON GMP'S ISSUED BY:

1) AUSTRALIA
2) THE UNITED STATES
3) THE WORLD HEALTH ORGANIZATION
4) THE UNITED KINGDOM
5) CANADA

THEIR DEPARTMENT OF HEALTH CONDUCTS ROUTINE INSPECTIONS TO ASSESS MANUFACTURER'S FACILITIES AND OPERATIONS AGAINST THE STANDARDS ESTABLISHED BY THEIR CODE. THIS CODE HAS NO STATUTORY FORCE. IT IS FOR THIS REASON, THAT THE CODE IS NOT RIGID AND IS "INTERPRETED" BY LOCAL INSPECTORS FOR INDIVIDUAL CASES.

THERE ARE VARIOUS NON-FDA STANDARDS THAT HAVE BEEN ACCEPTED TO CONTROL MANUFACTURING IN VARIOUS COUNTRIES IN EUROPE - THESE INCLUDE THE EUROPEAN FREE TRADE ASSOCIATION AND THE WORLD HEALTH ORGANIZATION. THESE REGULATORY GUIDELINES HAVE TO BE MARRIED WITH EACH INDIVIDUAL COMPANY'S GMP GUIDELINES FOR QUALITY ACCEPTANCE AND GOOD MANUFACTURING PRACTICE.

IN THE UNITED KINGDOM, THEIR MEDICINES INSPECTORATE OF THE DEPARTMENT OF HEALTH AND SOCIAL SECURITY (KNOWN AS DHSS), ISSUED AN "ORANGE GUIDE" FOR GOOD PHARMACEUTICAL AND MANUFACTURING PRACTICE.

THIS GUIDE, TOO, HAS NO STATUTORY FORCE, AND WAS DESIGNED NOT TO BE REGARDED AS AN INTERPRETATION OF THE REQUIREMENTS OF ANY ACT, REGULATION OR DIRECTIVE. THE PURPOSE OF THE U.K.'S ORANGE GUIDE IS TO OUTLINE STEPS THAT SHOULD BE TAKEN, AS NECESSARY AND APPROPRIATE, BY MANUFACTURERS OF MEDICINAL PRODUCTS, WITH THE OBJECT OF ENSURING THAT THEIR PRODUCTS ARE OF THE NATURE AND QUALITY INTENDED. THE REASON THAT THE U.K. CALLS IT THE "ORANGE GUIDE" IS BECAUSE THE COLOR OF THE COVER IS ORANGE!

LET US KEEP IN MIND THAT, ALTHOUGH THESE CODES HAVE NO "STATUTORY FORCE", THE LOCAL OPERATIONS MAKE EVERY EFFORT TO COMPLY WITH THE RECOMMENDATIONS MADE BY THEIR AUTHORITIES.

TOGETHER, THE GREEK MINISTER OF INDUSTRY AND ENERGY AND THE MINISTER OF SOCIAL SERVICES, ESTABLISHED STANDARDS OF GOOD MANUFACTURING PRACTICE FOR PHARMACEUTICAL PRODUCTS AS PUBLISHED IN THEIR GOVERNMENT GAZETTE OF THE HELLENIC REPUBLIC IN JANUARY, 1980. THESE GREEK GMP'S ARE SIMILAR TO THE BASIC STANDARDS OF GOOD MANUFACTURING PRACTICE FOR PHARMACEUTICAL PRODUCTS AS ISSUED BY THE EUROPEAN FREE TRADE ASSOCIATION (EFTA) UNDER THE CONVENTION FOR THE MUTUAL RECOGNITION OF INSPECTIONS FOR THE MANUFACTURE OF PHARMACEUTICAL PRODUCTS. THEIR GOAL IS TO PLACE THE GREEK PHARMACEUTICAL INDUSTRY ON THE SAME MANUFACTURING AND QUALITY CONTROL LEVEL AS THE EFTA PHARMACEUTICAL INSPECTION CONVENTION COUNTRIES, SUCH AS AUSTRIA, DENMARK, FINLAND, ICELAND, LICHTENSTEIN, NORWAY, PORTUGAL, SWEDEN, SWITZERLAND AND THE U.K.

IN SOUTH AMERICA, BRAZIL'S MINISTRY OF HEALTH ISSUED A GOOD MANUFACTURING AUDIT CHECKLIST OF SOME 300 QUESTIONS ON THE REGULATION AND INSPECTION OF PHARMACEUTICAL INDUSTRIES. THEIR COUNCIL ON MEDICINE AND PHARMACEUTICALS FOLLOWS THE GUIDELINES IN THE BRAZILIAN PHARMACOPOEIA, AND ESPECIALLY ADDRESSES SUBJECTS SUCH AS BIOLOGICAL QUALITY CONTROL.

IN ECUADOR, ENFORCEMENT OF PHARMACEUTICAL PRODUCTS IS BASED UPON REGULATIONS ISSUED BY THEIR NATIONAL INSTITUTE OF HYGIENE. THE GOVERNMENT USES LOCAL INSPECTORS TO OBTAIN SAMPLES OUT OF CUSTOMS AND HAVE THEM EVALUATED BY LOCALLY APPROVED LABORATORIES. INDUSTRIAL

PRODUCTION OF PHARMACEUTICAL PRODUCTS CAN ONLY BE PERFORMED, AT APPROVED PHARMACEUTICAL LABORATORIES, WHICH HAVE BEEN GIVEN LOCAL APPROVAL BY THEIR NATIONAL INSTITUTE OF HYGIENE.

IN ARGENTINA, PHARMACEUTICAL PRODUCTS MUST CONFORM WITH TESTS AND SPECIFICATIONS FROM THEIR ARGENTINE NATIONAL PHARMACOPOEIA OR OTHER RECOGNIZED PHARMACOPOEIAS WORLDWIDE.

THE SOUTH AFRICAN "DRUG CONTROL ACT" PROVIDES AN INSPECTION REPORT WHERE APPROXIMATELY 250 ITEMS ARE LISTED FOR REVIEW. LOCAL INSPECTORS UTILIZE THIS REVIEW LIST FOR THE ACCEPTABILITY OF A MANUFACTURING PROCESS AND THE PLANT AS A WHOLE.

THIS SOUTH AFRICAN SYSTEM IS BASED UPON A SERIES OF INSPECTION POINTS AWARDED FOR EACH OF THE ITEMS LISTED IN THE INSPECTION REVIEW. THE LOCAL AUTHORITIES FIND IT USEFUL, FOR FOLLOW-UP INSPECTIONS TO THESE FACILITIES, IN ORDER TO INDICATE TRENDS IN IMPROVEMENT OR IN DETERIORATION. IF THE SOUTH AFRICAN MEDICINE CONTROL COUNCIL FOUND THAT IMPROVEMENTS WERE NOT INDICATED, THEY HAVE HELD UP REGISTRATIONS OF NEW PHARMACEUTICAL PRODUCTS FOR SALE UNTIL THE IMPROVEMENTS WERE MADE.

NOW -- BLENDING THESE POINTS WITH THE QUALITY CONTROLLING FUNCTION --

AS YOU KNOW, A QUALITY PROGRAM SHOULD BE PART OF EVERY BUSINESS FUNCTION AND SHOULD INTEGRATE THE EFFORT INTO A MEASURABLE ADMINISTRATIVE PROCESS. THE ROLE OF QUALITY CONTROL IS TO PROVIDE AND COORDINATE A SYSTEM, WHICH ENSURES THE OPERATION TO PRODUCE AN OPTIMUM QUALITY PRODUCT, AT MINIMUM PRODUCT COST. RESPONSIBILITIES OF THIS QUALITY ORGANIZATION ARE TO DEFINE, PLAN, COORDINATE AND MEASURE THE QUALITY EFFORTS OF THE BUSINESS, AS WELL AS TO PERFORM THESE ACTIVITIES NORMALLY ASSOCIATED WITH QUALITY CONTROL. BECAUSE OF THE SUPPORT NATURE OF QUALITY CONTROL, AND SOMETIMES, THE LACK OF ADEQUATE MEANS TO RATE ITS PERFORMANCE, THE DIRECTIONS AND GOAL OF THE QUALITY PROGRAM MAY BE BASED UPON A PHILOSOPHY - RATHER THAN ON THE PERFORMANCE OF TASKS SUBJECT TO DIRECT MEASUREMENT.

QUALITY CONTROL FUNCTIONS SHOULD HAVE WELL-DEFINED RESPONSIBILITIES AND AUTHORITY, ALONG WITH ORGANIZATIONAL FREEDOM TO IDENTIFY, EVALUATE, AND PROVIDE SOLUTIONS TO QUALITY PROBLEMS. ONE CRUCIAL ASPECT FOR A SUCCESSFUL QUALITY PROGRAM IS MANAGEMENT ENDORSEMENT. SUCH ENDORSEMENT BY TOP MANAGEMENT DOES NOT AUTHORIZE THE QUALITY CONTROL ORGANIZATION TO RUN THE BUSINESS, BUT DOES IMPLY THAT THESE GOALS SHOULD BE AN INTEGRAL PART OF THE OVERALL OPERATIONAL PLANNING.

RECOMMENDATIONS FOR QUALITY IMPROVEMENT SHOULD BE VIEWED AS DIRECT PREVENTION OR COST REDUCTION. THEN, REAL COST OF SUCH A PROGRAM CAN BE MEASURED AGAINST THE ACTUAL COST REDUCED, AND FINAL SAVINGS REALIZED. PLACING A REALISTIC VALUE ON AN IMPROVED LEVEL OF QUALITY, SUCH AS REDUCED AND LESS COSTLY REWORK PROCEDURES, PRODUCTION DEFECTS CAUGHT AT THE EARLY STAGES, AND REDUCED WASTE, CAN RESULT IN LOWER LABOR COSTS AND REDUCED PRODUCTION DOWNTIME. KEEPING TO PRODUCTION SCHEDULES WILL REDUCE THE CREATION OF EMBARRASSING OUT OF STOCK STIUATIONS AND MAY ALSO RESULT IN LESS CONSUMER COMPLAINTS.

ONE CAN APPROXIMATE AND ESTABLISH THE COST OF A REJECTION BY THE RESULT OF A COST AVOIDANCE (AS IT IS KNOWN AS A RETURN INVESTMENT).

WHEN TOP MANAGEMENT SUCCUMBS TO THE PRESSURES OF MONTHLY SHIPPING SCHEDULES, IT IS QUITE UNDERSTANDABLE THAT THE QUALITY EFFORT MAY BE MISIDRECTED. IF A MUTUAL QUALITY PHILOSOPHY IS NOT ESTABLISHED BY BOTH QUALITY PERSONNEL AND TOP MANAGEMENT, THEN THE QUALITY PROGRAM DEGENERATES INTO A PERIODIC END OF THE MONTH PROGRAM INVOLVING DRASTIC SORTING, REWORKING, OR CONTINUAL CHANGING OF TOLERANCE STANDARDS. THIS LEADS TO PRODUCT EXPOSURES AND AN "OUT-OF-CONTROL" SYSTEM.

WHEN WE VISIT AFFILIATES, SUBSIDIARIES OR LICENSEES OUTSIDE THE UNITED STATES, WE TEND TO TAKE WITH US OUR OWN GUIDELINES OF PROPER QUALITY CONTROL FOR FACTORY OPERATIONS AND THEN UTILIZE THESE CONCEPTS IN OUR INTERACTIONS WITH OUR OVERSEAS PARTNERS. THIS MAY NOT BE CORRECT.

ONE ALWAYS HAS TO KEEP IN MIND THAT NO TWO FACTORY SITUATIONS ARE EVER EXACTLY ALIKE. IN JAPAN, THE LOCAL REGULATORY REQUIREMENTS MAY

BE INTERPRETED AS BEING MORE STRINGENT THAN WHAT IS FOUND IN THE UNITED STATES, THEREFORE, WE SHOULD ALWAYS WORK WITH WHAT IS REQUIRED IN TERMS OF OUR COMPANY REQUIREMENTS AND BLEND THAT WITH WHAT IS NECESSARY TO PRODUCE A QUALITY PRODUCT IN THAT SPECIFIC ENVIRONMENT.

THESE POINTS ARE BASED UPON WORKING WITH PEOPLE, ESTABLISHING PROPER ATTITUDES, AND INVOKING PROPER TRAINING IN ORDER TO ACCOMPLISH THE GOAL OF TRUE QUALITY CONTROL.

REALISTICALLY, WHEN A PHARMACEUTICAL REPRESENTATIVE FROM YOUR HOME OFFICE VISITS AN OVERSEAS AFFILIATE, FOR QUALITY CONTROL REVIEW AND AUDIT PURPOSES, WHAT SHOULD THEY REALLY LOOK FOR TO EVALUATE THE QUALITY PERFORMANCE OF THE ORGANIZATION? IN ADDITION TO THE "STANDARD" AUDIT CHECKLISTS THAT WE ALL HAVE, THERE ARE SEVERAL OTHER QUALITY-ORIENTED TASKS WHICH SHOULD BE LOOKED INTO.

YOUR REPRESENTATIVE SHOULD VISIT CONTRACT MANUFACTURERS, CONTRACT PACKAGERS AND INCLUDE VISITS TO THE VARIOUS FINISHED PRODUCT DISTRIBUTION CENTERS. HE WHOULD ALSO ASCERTAIN WHETHER THERE HAVE BEEN ANY CONSUMER COMPLAINTS IN THE LOCAL MARKETPLACE, REGARDING ANY OF THE PRODUCTS THAT HAVE BEEN MANUFACTURED OR PACKAGED AT THE LOCAL COMPANY OR BROUGHT IN AS FINISHED GOODS FROM OVERSEAS.

FOLLOW-UP WITH THE COMPLAINANT ENSURES GOOD CONSUMER RELATIONSHIPS. YOU CANNOT EXPECT COMPUTERIZED PRINT-OUTS OF CONSUMER COMPLAINTS FROM YOUR AFFILIATE IN THAILAND AS YOU MIGHT EXPECT FROM YOU LOCAL FACILITY IN CHICAGO, BUT IT SHOULD BE ORGANIZED AND AVAILABLE. THE QUALITY CONTROL REPRESENTATIVE SHOULD VISIT THE FIELD FOR THIS TYPE OF ACTIVITY, MAKE A REPORT, AND DISCUSS IT WITH THE LOCAL GENERAL MANAGER FOR FOLLOW-UP ACTION.

ADDITIONALLY, THE FIELD REPRESENTATIVE SHOULD FOLLOW UP WITH LOCAL MINISTRIES TO SEE IF THEY HAVE BEEN RECEIVING RE-REGISTRATION UPDATES IN TERMS OF THEIR VARIOUS REGISTERED PRODUCTS, AND EXHIBIT CONCERN OVER PENDING NEW REGISTRATIONS. ALSO, ANY CHANGES OR PENDING CHANGES IN LOCAL REGULATIONS SHOULD BE ASCERTAINED.

AS PART OF ESTABLISHING A PROPER QUALITY-ORIENTED OPERATION, A QUALITY CONTROL PROCEDURE MANUAL SHOULD BE AVAILABLE AT THE OVERSEAS FACILITY AND SHOULD INCLUDE SECTIONS ON:

1) RAW MATERIAL AND FINISHED PRODUCT TESTS AND SPECIFICATIONS
2) THE PRODUCT FORMULA
3) MANUFACTURING PROCEDURE AND DIRECTIONS FOR MAKING THE PRODUCT.
4) COMPONENT TESTS AND SPECIFICATIONS FOR PACKAGING THE PRODUCT.
5) STABILITY DATA
6) LABELLING TEXT DESCRIPTIONS ALONG WITH ANY SUPPORTABLE "CLAIMS" ON THE PRODUCT'S PERFORMANCE.

IT IS OUR RESPONSIBILITY TO PROVIDE LOCAL MANAGEMENT WITH INTELLIGIBLE GUIDELINES, DESIGNED TO END UP WITH THE BEST QUALITY CONTROL OPERATING UNIT FOR PRODUCTION GUIDANCE FROM BRANCH MANAGEMENT.

THE NEEDS IN ECUADOR AND PERU MAY BE DIFFERENT FROM THOSE IN BRAZIL OR IN THE UNITED KINGDOM. MINIMUM QUALITY STANDARDS SHOULD BE ESTABLISHED IN THESE PRODUCT MANUALS, WHICH ALL OPERATIONS SHOULD BE REQUIRED TO MEET. VARIOUS REFINEMENTS IN QUALITY CONTROL CAN BE ADDED LATER ON, SO THAT LARGER OR BETTER ORGANIZED COMPANIES CAN FOLLOW THESE PROCEDURES TO DEVELOP A MORE SOPHISTICATED OPERATION. THESE MANUALS AND SPECIFICATIONS SHOULD, OF COURSE, START WITH A BASIC QC PLATFORM TO MAKE THE ACTIVITIES OPERATIONAL AND REASONABLE, THEN EXPAND TO A SITUATION WITH REALISTIC GOALS.

MANY TIMES, WE WANT TO INTRODUCE, INTO AN OVERSEAS MARKETPLACE, A PRODUCT THAT'S CURRENTLY BEING SOLD IN THE UNITED STATES. WE PROCEED TO COUNT THE DOLLARS THAT WE ARE GOING TO ACCRUE FROM THIS INTRODUCTION AND THEN MAKE THE NECESSARY HEALTH REGISTRATION FILINGS IN ORDER TO GET THE PRODUCT ENTERED INTO THE MARKETPLACE. WHAT WE FAIL TO RECOGNIZE IS THAT PREPARING THIS PRODUCT LOCALLY FOR COST SAVINGS, AS OPPOSED TO BRINGING IN FINISHED GOODS, THERE SHOULD BE SIMILAR MANUFACTURING EQUIPMENT, ALONG WITH THE NECESSARY TECHNICAL EXPERTISE TO RUN IT, AND SIMILAR TEST EQUIPMENT TO ANALYZE IT. A COMPANY CANNOT

PROPERLY INTRODUCE A PRODUCT INTERNATIONALLY WITHOUT THE FULL KNOWLEDGE OF HAVING TO INVEST DOLLARS IN THE TECHNICAL AREA, IN ORDER TO GET THE YIELD THEY HAVE BEEN COUNTING ON.

FOLLOWING THIS, THEY CANNOT HOPE TO INTRODUCE A PRODUCT FOR WHICH AVAILABLE ANALYTICAL METHODOLOGY IS SOPHISTICATED, SUCH AS AUTO-ANALYZER, OR HIGH PRESSURE LIQUID CHROMATOGRAPHY, COUPLED WITH COMPUTER PRINT-OUTS FOR STATISTICAL EVALUATION, WITH THE KNOWLEDGE THAT ALL THE LOCAL LABORATORY HAS IS A COLORIMETER AND A WATER BATH, ACCOMPANIED BY ONE LAB MANAGER AND AN ASSISTANT. THIS IS AN IMPOSSIBLE SITUATION. WHAT IS NEEDED INITIALLY IS FORESIGHT AND PLANNING.

IF WE DO NOT HAVE CONTROL LABORATORY FACILITIES IN A PARTICULAR COUNTRY, AND ARE DESIROUS OF AVOIDING PROTRACTED DELAYS ASSOCIATED WITH THE SUBMISSION OF SMAPLES BACK HOME, IT IS INCUMBANT ON OUR PART TO MAINTAIN OUR QUALITY CONSCIOUSNESS, BY ENSURING THAT THE PRODUCT CAN BE MANUFACTURED AND TESTED PROPERLY AT A THIRD PARTY.

ALONG WITH THE NECESSARY SECRECY AGREEMENTS AND CONTRACTS WITH A THIRD PARTY ORGANIZATION, WE MUST DETERMINE THEIR WILLINGNESS TO ADHERE TO THE PRESCRIBED PROCEDURES IN THE MANUFACTURE OF OUR COMPANY'S PRODUCTS. WE MUST ALSO HAVE CONFIDENCE THAT THE MANUFACTURER'S INTEGRITY TO PRODUCE AND TEST OUR PRODUCT CAN BE ASSURED WITHOUT CONTINUAL APPROVAL FROM THE HOME COMPANY. DEPENDING UPON THE PRODUCT'S PROJECTIONS AND ACTUAL LOCAL PERFORMANCE, CONTINUATION WITH THE THIRD PARTY OR IN-HOUSE PRODUCTION PLANS SHOULD BE CONSIDERED.

REGARDLESS OF WHO DOES THE PRODUCT TESTING, THE ULTIMATE PRODUCT LIABILITY REMAINS OURS. FOR THIS REASON, ONE MUST CONSIDER IT ADVISABLE TO CHECK OUT THE THIRD PARTY ORGANIZATION'S PERFORMANCE IN REGARD TO QUALITY-PRODUCED BATCHES. IT IS ESPECIALLY IMPORTANT IN PRODUCTS WHERE THERE IS POTENTIAL MICROBIOLOGICAL CONTAMINATION.

A MECHANISM HAS BEEN ESTABLISHED WHEREBY THE MINISTRIES OF THE INDIVIDUAL COUNTRIES ADVISE THE WORLD HEALTH ORGANIZATION ABOUT ANY LOCALLY REPORTED MEDICAL REACTIONS IN PATIENTS, DEATHS, STABILITY OR MIX-UPS, ETC., ASSOCIATED WITH THE USE OF THESE DRUG PRODUCTS. IN

TURN, THE WORLD HEALTH ORGANIZATION NOTIFIES THE FDA SHOULD THE PRODUCTS BE TRACEABLE TO U.S. SOURCES. CONSIDERING THAT COMPLAINTS RECEIVED FROM ABROAD MAY NOT NECESSARILY BE CONFINED TO A PARTICULAR COUNTRY, THIS COULD CONCEIVABLY HAVE WORLDWIDE REPERCUSSIONS FOR A U.S. COMPANY'S REPUTATION AND TO THE STATESIDE STANDING OF A PARTICULAR PRODUCT.

IT IS CLEAR THAT THE VARIOUS GOVERNMENTAL MINISTRIES HAVE DIFFERENT PRACTICES IN ASSURING QUALITY OF PHARMACEUTICAL PRODUCTS PRODUCED IN THEIR COUNTRIES. CONSIDERING THIS, IT IS INCUMBANT ON OUR PART TO ENSURE THAT THE BEST GMP PRACTICES FOR PROPER QUALITY CONTROL ARE MAINTAINED ON THE LOCAL LEVEL, WITHOUT COMPROMISING STANDARDS WHICH COULD AFFECT THE HEALTH OF THE PUBLIC.

THIS IS OUR MUTUAL GOAL . . . TO ASSURE QUALITY IN OUR PRODUCTS ON A GLOBAL BASIS, UNIFORMLY AND CONSISTENTLY.

THANK YOU.