GROUP	NEG. SCAN NEG. X-RAY	POS. SCAN NEG. X-RAY	POS. SCAN POS. X-RAY	NEG. SCAN POS. X-RAY
Present study (51 cases)	68%	12%	16%	4%
Charkes et al (90 Cases)	44%	12%	39%	5%
DeNardo et al (114 cases)	23%	33%	39%	4%
Briggs (83 cases)	43%	20%	22%	1%

Scan appears to give earlier indication of bone involvement and extent than x-rays. Alkaline phosphatase values were of little aid in predicting Hodgkin's disease of bone because of concurrent liver disease that interfered with interpretations.

16. W. G. Weber et al (1968), Scintiscanning in malignant lymphomatous involvement of bone, Arch Int. Med. 121:433.

In 19 patients with malignant lymphoma bone scans with ^{85}Sr were positive in 16 cases and with x-ray only in two. Necropsy material obtained from vertebral bones with positive scans showed hissological evidence of disease in all six cases.

17. L. Rosenthall et al (1966) Role of Strontium-85 in detection of bone disease. Year Book of Nuclear Med. Vol. 1, pp 359-361.

A short review pointing out that any abnormalities causing increased calcium accretion will be reflected in an increased ^{85}Sr uptake and these include benign tumors, fractures, osteomyelitis, degenerative arthritis, Paget's disease, hyperostosis frontalis interna, ankylosing spondylitis, surgical osteomy, fibrous dysplasia, osteochondromatosis and growing epiphysis.

18. G. C. H. Bauer (1968), Clinical use of radioactive isotopes in orthopedics, Cornell Vet. Suppl. 58:149.

A long rambling work presenting mostly results with ^{85}Sr and ^{47}Ca obtained from open literature.

20. R. M. Hodges et al (1950) The strontium content of human bones, J. Biol. Chem. 185:519.

The strontium content of bone was on the average 0.024 percent.

21. N.S. MacDonald et al (1962), The bidirectional transport of radiostrontium across the primate placenta. Radiation Res. 17:752.

In two pregnant rhesus monkeys it was shown that strontium administered in tracer doses rapidly transverses placental membrane in both directions and was deposited in both maternal and fetal bone.

22. J. Rivera (1963), Strontium - calcium discrimination by the human placenta Nature 200:269.

Strontium concentration in fetal serum was somewhat less than in maternal serum, 0.036 versus 0.045 micrograms/ml.

Note: References numbers 23 to 27 deal with animal studies and ^{85}Sr metabolism in pregnancy.

28. G. L. DeNardo et al (1967), Radioisotope skeletal survey, J.A.M.A. 200:11.

In 49 patients with malignant neoplasms whole-bone profile scans (one demensional scanning of body with activities and positions recorded on profile curves) were done 24-72 hrs. after I.V. ^{85}Sr. According to authors this technique proved more sensitive than photoscanning or x-ray skeletal survey. No folse negatives or false positives were noted. The principal advantage of profile scanning is the reduction of time needed for a bone survey to 10-15 minutes.

30. E. Smith (1966), Calculating absorbed doses for radiopharmaceuticals Nucleonics 24:33-40.

Modes of calculating radiation dosages to body are presented, the marked differences in values obtained with methods using absorbed fraction and geometric factor are pointed out. The greatest source of uncertainty of absorbed dose calculations are due to uncertainties in biological distribution and normal variability.

31. E. H. Quimby (1960), Some problems regarding permissible doses with radioactive isotopes, J. Nucl. Med. 1:14.

A general review paper on permissible radiation dosages to patients and health personnel.

32. R. A. Seltzer et al (1964), Radiation exposure from radioisotopes in pediatrics New England J. Med. 271:84.

The average radiation doses to whole body and selected of normal children and "standard man" are claculated for tests using radionuclides. It was stressed that an infant or child may sustain an average whole-body dose up to 20 times that of standard man. However the average whole-body doses due to procedures with radionuclides are often less than those sustained during routine fluoroscopic or radiographic studies (190-480 millirads in one year old children and 970-1400 millirads in standard man). Because of deficiency in metabolic data for children calculation were usually based on data from adults.

33. N. D. Charkes et al (1963) The pathologic basis of the strontium bone scan, J.A.M.A. 206:2482.

Bone biopsies were obtained from 30 cancer patients who had been scanned 1-15 days after receiving 20-100 microcuries ^{85}Sr I.V. In 15 cases ^{85}Sr concentrations of specimens were measured. ^{85}Sr concentrations increased where actively proliferating new bone was formed in response to tumor invasion and scan was abnormal. Phases I and II in authors' classification. But when reactive bone formation was absent the scans and ^{85}Sr were normal and may be associated with radiodensities (completion of bone repair, phase III) or radiolucencies (tumor-laden bone with now new formation, 5 patients presented.) Tumor cells were found in specimens from biopsy and autopsy in 22/28 pts. with abnormal scans, and in 8/12 from pts with normal x-rays and abnormal scans.

34. M.P. Papworth et al. (1967), Localization of bone disease with radiostrontium J. Nucl. Med. 8:723.

In 56 pts. serial counts were made over selected bone sites (selection dependent on clinical and radiographic considerations) five times over a period of 96 hours after 20 microcuries of ^{85}Sr. Determinsations of uptake and retention of Sr-85 in bone lesions may reveal metastatic involvement months before radiographs. In a series of 46 pts. ^{85}Sr findings were positive in 19 and negative intwo when x-rays were positive; and positive in 17 and negative in 8 patients when the x-rays were negative.

35. N.D. Charkes et al (1964), Detection of metastatic cancer to bone by scintiscanning with ^{87m}strontium Amer. J. Roent. Rad Therapy and Nucl. Med. 91:1121.

A study in 16 pts with ^{87m}Sr 6 of which also received ^{85}Sr. Identical bone scans were obtained in latter group. The advantage of ^{87m}Sr is that with its shorter half life, 2.8 hours, the radiation dose is much less (2.4 millirads to whole body for 100 microcuries).

36. D.M. Sklaroff and N.D. Charkes (1967), Early detection of bone lesions by photoscanning with radioactive strontium. Cancer 20:737

A general paper on the authors favorable experience with photoscanning using ^{85}Sr in over 500 patients.

37. J. Kereiakes et al (1968), Radiopharmaceutical dosimetry in pediatrics. Radiology 90:925.

A paper of dubious value comparing 'observed'(?) and calculated radiation doses to whole body and thyroid of children. How the 'observed' radiation dosages were calculated was not explained but they were supposedly derived from whole body thyroid counts.

38. R. Spencer et al (1967), Bone scanning with ^{85}Sr, ^{87m}Sr and ^{18}F Brit. J. Radial 40-641-654.

A long paper of the authors' experience with the above radionuclides in 50 patients. In primary and metastatic bone lesions it was claimed that scanning gives a more accurate and earlier assessment of radiotherapy field size than does the radiograph, thus confirming similar reports of other investigators. According to their calculations radiation does of 70 microcuries ^{85}Sr to whlle body is 1.6 REMS and to bone 3.1. The corresponding values for 3 millicuries of ^{87m}Sr are 0.02 and 0.3; for 2 millicuries ^{18}F, 0.07 and 0.36 REM resp.

Conclusions:

1. Clinical studies by the firm and from the open literature provide sufficient evidence that ^{85}Sr Strontium nitrate is effective in detecting bone lesions or milignancies when used under proper conditions.

2. The absence of clear-cut adverse reactions associated with ^{85}Sr despite wide spread use would seem to indicate a relative safety although the long term effects of the relatively high radiation dosages (for 100 microcuries 0.6 rads to whole body and up to 4.6 Rad to bone) remain to be seen.

3. The insert as proposed is inadequate.

Recommendation:

Send letter to firm declaring application not approvable. In letter include the 15 requests for changes in package insert (in quotations under evaluation of insert as given above).

E. H. Chacalos, M.D.

Addendum:

In the opinion of Dr. B. Jones, Deputy Director, a non-approvable letter should not be sent. He prefers to settle the deficiencies in the insert by telephone or in a conference with representatives of the firm.

E. H. Chacalos, M.D.

cc:
Orig., ~~Dup., Trip.~~
BD-100, BD-150
BD-150:EHChacalos:6/24/71
Final typed by slt:7/13/71

SUBSEQUENT MEDICAL SUMMARY OF NDA 17-024

NDA: 17-024 March 29, 1973

Applicant: E. R. Squibb & Sons, Inc.
New Brunswick, New Jersey

Name of Drug: Trade: Strotope

Generic: Strontium Nitrate Sr-85

Type and Date of Submission: NDA original amendment with revision of package insert.

Clinical Review: Revised package insert (dated March 8, 1973) was submitted in response to telephone conversation (dated March 5, 1973) requesting three changes in package insert as set out in medical summary dated March 2, 1973. In present insert the indications statement under actions section has been deleted and comparative F-18 radiation doses have been added. The statement dealing with repeated use of Sr-85 has not been deleted but rewarded to read:

., DRAFT LABELING

[redacted]

This rewording more or less weapens our objections and the reasons for requesting deletion and is now acceptable.

Conclusion:
1. Firm has complied sufficiently with requests to change insert.
2. Application is approvable.

Recommendation: Send approvable letter.

E.H. Chacalos, M.D.

cc:
NDA 17-024 Orig. Dup. Trip.(NYK-DO)
BD-100
BD-150, BD-150/EHChacalos:3/29/73
R/D Endorsed by BLJones:3/29/73
Final typed deg:4/9/73

SUBSEQUENT MEDICAL SUMMARY OF ORIGINAL NDA # 17-024

March 2, 1973

NDA 17-024

APPLICANT: E. R. Squibb & Sons, Inc.
New Brunswick, New Jersey

Name of Drug: Trade- Strotope

Generic: Strontium Nitrate
Sr-85 Injection

Type and Date of Submission: Amendment to original NDA dated December 19, 1972 (Label revision). Amendment dated January 26, 1973 deals with validation samples and controls.

Chemistry Summary

Pharmacology Summary: Summary dated December 30, 1971 (Hein) concludes NDA remains approvable with minor changes in labelling.

Clinical Review:
Amendment dated 12/19/72 is in response to FDA letter dated 7/18/72 suggesting revision of package insert in accord with sample insert prepared in conjunction with FDA Radiopharmaceutical Advisory Committee. The submitted insert (dated 12/15/72) was compared with sample insert and the two were found to differ in several aspects, some of which are acceptable, some not.

DRAFT LABELING

However three changes are not acceptable. These are listed below:

1. The statement under Actions reading DRAFT LABELING

Reason: This is strictly speaking an indication and an unacceptable one at that. Sr-85 may detect areas of altered osterogenic activity or bone lesions but to determine whether these are tumours or no necessitates additional procedures. Hence this addition is unacceptable.

2. Under Precautions delete the added paragraph reading [redacted] DRAFT LABELING

Reasons: This paragraph is unacceptable because it implies guardedly that additionals doses may be given at suitable. This is questionable and open to debate. If done three serve in one year this would exposure the radiosensitive bone marrow to up to 18-21 rads. This could also include children which are not explicitly excluded from receiving Sr-85 in insert.
If such studies should need to be repeated it would perhaps be wise to use a bone scanning agent with a lesser radiation burden to the bone marrow.

3. "Under Radiation dosimetry the comparative radiation doses of F-18 (1 mCi) to whole body and skeleton have been deleted and should be reinsected."

Reasons: F-18 radiation doses were added to indicate the comparative radiation hazard of Sr-85 and is a question of comparative safety not efficacy. Detailed reasons are given in medical summaries of [redacted]

Conclusions: 1. NDA is not approvable because three major unacceptable deviations from sample package insert.
2. Several other changes were made in package in wordings as well as in content which were deemed acceptable.

Recommendation: Send letter to firm stating that package insert is not acceptable and listing the three deficiencies noted above.

E.H. Chacalos, M.D.

cc:
NDA 17-024 Orig., Dup., Trip.(NYK-DO)
BD-100, BD-150
BD-150/EHChacalos:3/2/73
R/D Endorsed by BLJones:3/6/73
Final typed deg:3/9/73

Addendum (March 5, 1973)

Dr. N. W. Lavy, Director of Drug Regulatory Affairs for the firm was contacted by telephone on March 5, 1973 and the package insert discussed. The three unacceptable changes in package insert listed above were read to him verbatim over the phone. He argued strongly against the request to delete the precaution limiting Sr-85 use to four month periods. He was also not too receptive to the idea of including comparative radiation doses for F-18. It was pointed out to him that it was a question of relative safety, not relative efficacy, and that our advisory committee had recommended the comparison. He said he would have to discuss these matters with his legal people and those who wrote the package insert. He was told that the other deviations from the sample insert were acceptable as far I was concerned. Asked whether he was welling to commit himself to accepting the three requested changes he replied he could not without closer study and internal discussion with his staff. He said he would communicate with FDA either by mail or conference when the matter is settled.

E.H. Chacalos, M.D.

REVIEW OF NDA #17-024

NDA: 17-024 April 6, 1972

Applicant: E. R. Squibb & Sons, Inc.
New Brunswick, New Jersey

Drug: STROTOPE (Strontium Nitrate Sr 85 Injection)

Review confined to resubmission section replying to notification letter of August 17, 1971.

1. Radiopurity has been adequately clarified.

2. A. Immediate Container label appears adequate.

   B. Lead pig label - this label is acceptable.

   C. Variable Data Assay Sticker.

      This looks adequate - it resolves earlier question regarding expiration dating.

3. Package Insert

Description: Delete "and prognostic". DRAFT LABELING [redacted]

Physical Properties: Acceptable as written.

Actions: The final sentence is an overstatement, in my opinion. It should be deleted or supported by bibliographic entry. It does not really relate to action.

Indications: In last sentence of first paragraph substitute DRAFT LABELING DRAFT LABELING final phrase "^{85}Sr uptake may occur in ---". Also insert [redacted] in place of [redacted] in the same sentence. I suggest delete first sentence of the second paragraph. This is prognostication based on flimsy evidence. I would not take exception to its (Sr-85) being claimed as useful for staging malignant disease known to be bone seeking such as breast cancer or prostatic cancer. No other exceptions found.

Warnings: Acceptable as submitted.

Precautions: Acceptable as submitted.

Adverse Reactions: Acceptable as submitted.

Dosage and Administration: I question the "usual I.V. dose as tested at 50 uCi (range 50-100 uCi) for adults" -- I have never used doses less than 100 uCi in adults and do not know anyone who has - - and successfully imaged the boney structure desired.

Recommend usual dose of 100 uCi with range of 50-125 uCi for adults. Child's dose should be scaled down by body weight. Range could be 1 to 2.5 uCi/kg.

Dosimetry: This section might be improved by use of data from MIRD supplements.

Guidelines for photoscanning.

Time of scanning: Acceptable

Preparation of the patient: Acceptable

Position: Acceptable - but could be improved by specifying prone as position used for pelvic and lumbar spine scanning when single over-the-table scintellation detector is used.

How Supplied: Acceptable

References: Acceptable

Recommendation: Acceptable resubmission with modifications noted herein with regard to the product insert.

/S/ [redacted]

J. K. Goodrich, M.D.

cc:
NDA 17-024 Orig. Dup.
NYK-DO
BD-150
BD-100
BD-150/JKGoodrich:sea 4/7/72

ADDENDUM TO REVIEW OF NDA 17-024

NDA: 17-024 April 13, 1972

Conference with two representatives of the sponsor resolved the areas of exception listed in this review.

/S/ [redacted]

J. K. Goodrich, M.D.

cc:
NDA 17-024 Orig. Dup.
NYK-DO
BD-100
BD-150
BD-150/JKGoodrich:sea 4/13/72

APPEARS THIS WAY ON ORIGINAL