

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208143Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208143
Supporting document/s: 001
Applicant's letter date: December 18, 2014
CDER stamp date: December 18, 2014
Product: READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE,
2% barium sulfate suspension (w/v)
Indication: For Use in Computed Tomography of the
Abdomen [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
Applicant: BRACCO DIAGNOSTICS, INC.
Review Division: Medical Imaging
Reviewer: Ronald Honchel, Ph.D.
Supervisor/Team Leader: Adebayo Laniyonu, Ph.D.
Division Director: Libero Marzella, M.D., Ph.D.
Project Manager: Frank Lutterodt

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

Although not FDA approved, barium sulfate has been used since the early 1900's as a positive contrast agent for radiographic studies. Barium sulfate has a high molecular density relative to soft tissues allowing for increased X-ray absorption and delineation of the gastrointestinal (GI) tract. The Sponsor stated that the safety and efficacy of barium sulfate imaging products have been well established with more than a 100 years of clinical use experience. The Sponsor and DMIP recently agreed to submitting 505(b)(2) NDA applications (this application being the second) based on the publically available data for the barium sulfate containing products marketed by the Sponsor.

1.2 Brief Discussion of Nonclinical Findings

The LD₅₀ of intragastrically administered barium sulfate (150% w/v) was calculated to be 364 g/kg in young (130-160 g) male CBL-Wistar albino rats. The cause of death was stomach rupture. No other relevant nonclinical studies or findings for barium sulfate were reported in the literature. Thus, nonclinical cannot recommend approval of this NDA application from a discipline perspective due to the lack of nonclinical data. Nonetheless, there is extensive clinical experience with barium sulfate. If clinical determines that there is adequate clinical safety data to support approval; nonclinical will concur.

The Sponsor refers only to barium sulfate in their proposed nonclinical labeling sections. The Nonclinical Reviewer proposes using the drug product name (READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE) instead of barium sulfate due to the numerous potential impurities present in the drug product. The amount of barium sulfate potentially present at the highest recommended dose for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE (18.9 g) is much less ^{(b) (4)}fold less) than that present in E-Z-HD[™] (340 g). As a result, the amount of ^{(b) (4)} (the two impurities present in ^{(b) (4)} that are the most concern in regards to pregnancy labeling) potentially present in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE is ^{(b) (4)}fold less than that potentially present in E-Z-HD. While there is nonclinical and clinical evidence to support the safety of the proposed use of barium sulfate containing drug products in adults, there is little data on the effect of barium sulfate, and no data on the effect the impurities present in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE may have on pregnancy, carcinogenesis, mutagenesis, and fertility. Furthermore, while one could postulate that the risks for the oral administration of barium sulfate during pregnancy are likely low, there is little or no evidence to support a similar determination for some of the impurities present in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE. The Nonclinical Reviewer also proposed removing language that is not supported by data or has not been adequately evaluated (i.e. the Sponsor's statement that ^{(b) (4)}). The remaining nonclinical proposed changes were made to follow the format typically used by the Division in the past.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, NDA approval should be based on the adequacy of the available clinical safety data for which nonclinical defers to clinical.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Proposed by the Sponsor:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Proposed by Nonclinical using current labeling rules:

8.1 Pregnancy

(b) (4)

Of note, applications submitted after June 30, 2015 must follow new Pregnancy Labeling Rules. The Division has decided to follow this new labeling rule for the barium sulfate NDAs including NDA 208143. The new rule states that if data demonstrates that the drug is not absorbed systemically, the "Risk Summary" must contain only a specified statement regarding this fact. The drug for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE contains not only barium sulfate (not absorbed systemically) but many impurities including heavy metals such as (b) (4). Thus, the above pregnancy labeling language is recommended even with the new pregnancy labeling rule.

Proposed by the Sponsor:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the carcinogenic potential of barium sulfate or potential effects on fertility. (b) (4)

Proposed by Nonclinical:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies have not been performed to evaluate the carcinogenic potential of READI-CAT[®] 2 or READI-CAT[®] 2 SMOOTHIE. The mutagenic potential of READI-CAT[®] 2 or READI-CAT[®] 2 SMOOTHIE has not been evaluated. The effect of READI-CAT[®] 2 or READI-CAT[®] 2 SMOOTHIE on fertility has not been evaluated.

2 Drug Information

2.1 Drug

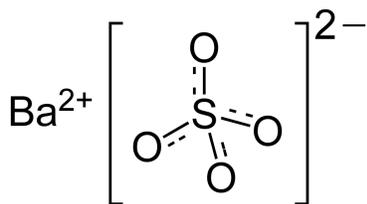
CAS Registry Number: 7727-43-7

Code Name: READI-CAT[®] 2 or READI-CAT[®] 2 SMOOTHIE

Chemical Name: Barium sulfate

Molecular Formula/Molecular Weight: BaSO₄/233.39

Structure:



Pharmacologic Class: Radiographic contrast agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

None.

2.3 Drug Formulation

READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE consists of 450 mL barium sulfate suspension (2% w/v) in a (b) (4) mL high density polyethylene bottle. The READI-CAT[®] 2 composition is shown in the Sponsor's Tables below.

Table A: Readi-Cat 2 Drug Product Composition

Component Number	Component Name	% w/v	Function	Grade
(b) (4)	Barium sulfate (b) (4)	2.0898	Contrast Agent (b) (4)	USP
	Xanthan Gum			NF
	Simethicone Emulsion			USP
	Potassium Sorbate			NF
	Sodium Benzoate			NF
	Citric Acid (b) (4)			USP
	Sorbitol Solution			USP
	Saccharin Sodium			USP
	Natural and Artificial Orange flavor ^a			N/A
	Natural and Artificial Vanilla flavor ^b			N/A
	Purified Water			USP (b) (4)

Table A: Readi-Cat 2 Smoothie Drug Product Composition

Component Number	Component Name	Function	Grade	Composition % w/v			
				Banana	Creamy Vanilla	Berry	Mochaccino
(b) (4)	Barium sulfate (b) (4)	Drug Substance (b) (4)	USP	2.0898	2.0898	2.0898	2.0898 (b) (4)
	Xanthan Gum		NF				
	Simethicone Emulsion		USP				
	Potassium Sorbate		NF				
	Sodium Benzoate		NF				
	Benzoic Acid		USP				
	Citric Acid (b) (4)		USP				
	Sodium Citrate		USP				
	Sorbitol Solution		USP				
	Purified Water (b) (4)		USP				
	Saccharin Sodium		USP				
	Artificial Vanilla Flavor (b) (4)		Food Grade				
	Naturally (b) (4) Banana Flavor	Food Grade					
	Natural and Artificial Blueberry Flavor (b) (4)	Food Grade					
	Natural and Artificial (b) (4) Chocolate Flavor	Food Grade					
	Natural and Artificial Coffee (b) (4) Flavor	Food Grade					

2.4 Comments on Novel Excipients

There are no novel excipients used in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE.

2.5 Comments on Impurities/Degradants of Concern

The barium sulfate drug substance contains a number of impurities. The Sponsor proposed impurity limits and provided an expert opinion toxicology report to support the

safety of those proposed limits. From the Nonclinical Reviewer's perspective, the only firm conclusion one could make for some of the evaluations provided in the expert opinion toxicology report was that the proposed impurity limit was "probably safe" as the data for some of the impurities was limited and the methods used for determining safety were inconsistent. Nonetheless, the impurity limits proposed by the Sponsor seem reasonable given that barium sulfate has been around so long. For example, the impurity limit set for (b) (4) in the drug substance was set at NMT (b) (4) % w/w. The (b) (4) levels in 13 recent batches of drug substance ranged from (b) (4) % to (b) (4) %. While the information provided in the expert opinion document supported that a (b) (4) % w/w impurity limit for (b) (4) is probably safe, that (b) (4) % and greater (b) (4) is apparently common in the drug substance strongly supports the safety of the NMT (b) (4) % limit.

2.6 Proposed Clinical Population and Dosing Regimen

As stated in the draft labeling, READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE is indicated for use in adults for use in Computed Tomography of the abdomen (b) (4).

The typical adult dose is 450-900 mL (9 (4)-18 (4) g barium sulfate).

2.7 Regulatory Background

The Sponsor and DMIP recently agreed to submitting 505(b)(2) NDA applications based on the publically available data for a number of the barium sulfate containing products marketed by the Sponsor. This NDA for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE is the second of those products to be submitted to the FDA.

3 Studies Submitted

3.1 Manuscripts Reviewed

McCauley PT, Washington JS. Barium bioavailability as the chloride, sulfate, or carbonate salt in the rat. *Drug Chem Toxicol.* 1983, 6(2): 209-217.

U.S. Environmental Protection Agency. EPA/635/R-05/001. Toxicological review of barium and compounds. Revised on June 2005.

Boyd EM, Abel M. The acute toxicity of barium sulfate administered intragastrically. *Canad. Med. Ass. J.* 1966, 94: 849-853.

3.2 Manuscripts Not Reviewed

Shackleton KL et al. Effect of barium sulfate on wound healing in the gastrointestinal tract of the rat. *Radiology* 2000, 214(2): 563-567.

Maglinte DD et al. The effect of barium enemas and barium sulfate on healing of colorectal biopsy sites. *Dis. Col. & Rect.* 1983, 26(9): 595-597.

Kozianka J et al. Barium Peritonitis – a Study in Pigs. *Adv. Clin. Exp. Med.* 2003, 12(5): 569–573.

Pucci C et al. Barium peritonitis: experimental study using barium sulfate and radioactive barium. *La radiologia medica.* 1983, 69 (1-2): 7-10.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

The Sponsor stated that there was no primary pharmacology data available in the literature.

4.2 Secondary Pharmacology

The Sponsor stated that there was no secondary pharmacology data available in the literature.

4.3 Safety Pharmacology

The Sponsor stated that there was no safety pharmacology data available in the literature.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

McCauley PT. Washington JS. Barium bioavailability as the chloride, sulfate, or carbonate salt in the rat. Drug Chem Toxicol.1983, 6(2): 209-217.

Objective: This study was conducted to determine how the bioavailability of low concentration barium (Ba) in the drinking water is affected by the anion.

Methods: Male 250-300 g Sprague Dawley rats were maintained on a low barium diet (less than 1 mg Ba/kg of food) for at least one month. Non-fasted rats were then administered via intubation 0.5 mL/100 g body weight of a solution containing 10.0 mg ¹³¹Ba/L in the sulfate, chloride, or carbonate salt form. Animals were sacrificed 2, 5, 10, 30, 60, and 120 min and 24 hr after dosing. ¹³¹Ba levels were determined in the blood and eye at these timepoints in all groups, whereas radioactivity levels in heart, kidney, liver, and skeletal muscle were determined at 24 hr after dosing in the chloride salt group only. The above study was also performed in fasted (beginning 24 hr prior to dosing) animals administered the chloride salt except the final timepoint being 4 hr after dosing and only blood and eye radioactivity levels were evaluated.

Results: When the chloride salt was administered, blood ¹³¹Ba levels increased linearly for the first 10 min, then less rapidly until peaking at 60 min. Blood ¹³¹Ba levels were still 90 % of those observed at peak at 24 hr after dosing. The heart had the highest ¹³¹Ba levels (8x that observed in the blood) at 24 hr after dosing followed by the eye, skeletal muscle, kidney, and liver. When the sulfate and carbonate salts were administered, blood ¹³¹Ba levels were ~85% and ~45% of that observed for the chloride salt. Fasting altered the absorption of radioactivity for the chloride salt. Blood

radioactivity levels were higher compared to non-fasted rats peaking at 10 min after dosing (peak radioactivity levels were about 20% higher in fasted compared to nonfasted rats), but declined steadily afterwards until the blood radioactivity level was ~50% of peak level at 4 hr after dosing. Eye radioactivity was increased in fasted compared to nonfasted rats.

Nonclinical Reviewer's conclusions: The manuscript stated that Ba concentration in certain ground water aquifers exceeds ^{(b) (4)} mg/L. The objective of the study was to mimic natural environmental exposure to barium salts in the drinking water. This study is not relevant for evaluating the safety of READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE because the barium salt dose levels used were markedly lower (5 µg Ba/kg) compared to that used clinically for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE (the dose would be 0.32 g Ba sulfate/kg if a 60 kg person is administered 900 mL of READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE). Nonetheless, this and other studies suggest that unlike high dose oral administration, a large fraction (similar to that observed with highly bioavailable barium chloride) of orally administered Ba is absorbed when the barium sulfate dose is low.

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

Boyd EM, Abel M. The acute toxicity of barium sulfate administered intragastrically. Canad. Med. Ass. J. 1966, 94: 849-853.

The LD₅₀ of intragastrically administered barium sulfate (150% w/v) was calculated to be 364 g/kg in young (130-160 g) male CBL-Wistar albino rats. The cause of death was stomach rupture.

6.2 Repeat-Dose Toxicity

The Sponsor stated that there was no repeat-dose toxicity data available in the literature.

7 Genetic Toxicology

The Sponsor stated that there was no genetic toxicology data available in the literature.

8 Carcinogenicity

The Sponsor stated that there was no carcinogenicity data available in the literature.

9 Reproductive and Developmental Toxicology

The Sponsor stated that there was no reproductive and developmental toxicology data available in the literature.

10 Special Toxicology Studies

There was no special toxicology relevant data available in the literature.

11 Integrated Summary and Safety Evaluation

Although barium sulfate has been used clinically since the early 1900's as a positive contrast agent for radiographic studies, there was only one manuscript available that was relevant for evaluating the approvability of barium sulfate from a nonclinical perspective. As reported by Boyd et al. (Canad. Med. Ass. J. 1966), the LD₅₀ of intragastrically administered barium sulfate was calculated to be 364 g/kg in young male rats. The cause of death was stomach rupture. The Sponsor did submit an EPA report titled "Toxicological Reviews of Barium and Compounds"; however, the EPA report primarily dealt with environmental barium exposure and was not generally relevant to evaluating the safety of barium sulfate when used as a contrast agent.

Barium sulfate is biologically inert (thus not metabolized) and systemic barium sulfate is eliminated unchanged mainly in the feces and urine. Although generally poorly absorbed, statistically significant increases in blood and urine barium levels has been reported in humans after ingesting 58 to 400 g barium sulfate in radiopaque contrast materials (Claval et al., *Therapie* 1987; Mauras et al., *Therapie* 1983). The Sponsor routinely states that barium sulfate absorption is negligible; however, the Sponsor did not provide adequate data to support this statement. Nonetheless, there is strong evidence that barium absorption is relatively low following high dose oral administration of barium sulfate with no additional absorption observed with increasing barium sulfate dose once the ability of gastric acid to liberate barium ions has been exceeded. Additionally, there are no nonclinical concerns with the inactive ingredients (sorbitol, xanthan gum, simethicone emulsion, etc.) present in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE.

Nonclinical cannot make a recommendation that this NDA application should be approved based on the nonclinical data due to the lack of nonclinical data. As described in the previous paragraph and based on the review of the McCauley & Washington manuscript, there is likely some systemic exposure to barium following the oral administration of barium sulfate. Published reports/studies on the ingestion of more soluble barium salts clearly indicate that toxicity will be observed if enough barium is absorbed. Neither barium absorption at clinically relevant barium sulfate doses nor the blood/tissue barium levels that produce toxicity have been adequately evaluated.

Nonetheless, there is extensive clinical experience with barium sulfate. From a nonclinical perspective, the drug product is approvable from a safety standpoint if clinical determines that there is adequate clinical safety data to support approval.

The Sponsor refers only to barium sulfate in their proposed nonclinical labeling sections. The Nonclinical Reviewer proposes using the drug product name (READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE) instead of barium sulfate due to the numerous potential impurities present in the drug product. Of particular concern is that while one could postulate that the risks for the oral administration of barium sulfate during pregnancy are likely low, there is little or no evidence to support a similar determination for many of the impurities present in READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE. Applications submitted after June 30, 2015 must follow new Pregnancy labeling rules. The Division has decided to follow this new labeling rule for the barium sulfate NDAs including NDA 208143. The new rule states that if data demonstrates that the drug is not absorbed systemically, the “Risk Summary” must contain only a specified statement regarding this fact. The Pregnancy labeling proposed by DMPH states that READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE is “not absorbed systemically by the mother following oral administration, and maternal use is not expected to result in fetal exposure to drug”. From the Nonclinical Reviewer’s perspective, this is not an accurate statement because the drug for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE is the (b) (4) contains not only barium sulfate (not absorbed systemically) but also many impurities. Most of the impurities are inert or are present in amounts that are probably safe based on the fact that they can also be present in similar quantities in water sources, foods, drugs, etc. There are 2 impurities that are potentially concerning in regards to pregnancy. The highest recommended dose for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE could contain (b) (4) g of (b) (4) and (b) (4) mg of (b) (4) and still be within set impurity limits. There is little or no data to support a statement that these 2 impurities are not absorbed systemically by the mother and administration of READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE would not result in fetal exposure to (b) (4). READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE are administered in conjunction with radiation (Computer Tomography) and the concerns with radiation exposure during pregnancy are well documented. Similar to radioactive diagnostic agents, nonclinical reproductive toxicology studies are not recommend for READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE since it’s use would already be counter-indicated during pregnancy due it’s use in conjunction with radiation. Nonetheless, the Nonclinical Reviewer recommendation is to, at a minimum, state in the labeling that reproductive toxicology studies have not been performed and the risks of READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE during pregnancy are unknown so as not to give the impression that there are no potential risks with the administration READI-CAT[®] 2 and READI-CAT[®] 2 SMOOTHIE during pregnancy.

12 Appendix/Attachments

None.

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/s/

RONALD HONCHEL
07/23/2015

ADEBAYO A LANIYONU
07/23/2015

I agree with Dr. Honchel that nonclinical cannot recommend approval of this NDA application from a discipline perspective due to the lack of nonclinical data. Nonetheless, there is extensive clinical experience with barium sulfate. If clinical determines that there is adequate clinical data to support approval, nonclinical concurs. Dr. Honchel comments and recommendations on labeling are noted. Labeling language consistent with the Pregnancy and Lactation Labeling Rule is being made at the review team level

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208-143 **Applicant:** Bracco Diagnostics Inc. **Stamp Date:** December 18, 2014

Drug Name: Readi Cat-2 **NDA/BLA Type:** 505(b)2
Smoothie (Barium Sulfate)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. As a 505(b)2 application the Sponsor is relying on publically available literature.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A. See above.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A. See above.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The labeling to be recommended for this application will determined in future labeling meetings.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	Nonclinical will be relying on CMC to identify any potential impurity issues, but the potential for impurity issues would seem remote since the product has been used clinically for over 100 years.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

RONALD HONCHEL
02/11/2015

ADEBAYO A LANIYONU
02/11/2015