DANGEROUS DRUGS IN YOUR MEDICINE CABINET?
A WHISTLEBLOWER’S ACCOUNT OF INDIA’S TROUBLING EXPORTS

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ROGER BATE: Well, good morning. Good morning, ladies and gentlemen. Thank you very much for coming. Sorry we’re starting a little late. Dinesh was in demand by the media, as he always is, wherever he goes.

We do in fact have four people on this panel. Harry Lever from the Cleveland Clinic is joining us by the miracles of modern technology, via video conference. He couldn’t leave his patients – that’s how good a doctor he is – in Ohio. It’s a clinic day and he – but he is joining – he will be joining us after Dinesh’s remarks.

What we will do is Dinesh will speak, and then I’ll have our other two contributors speak. And then I’ll probably ask them a few questions. We’ll have a discussion and then I’m going to open it up to the – to the floor.

It’s a great pleasure to introduce Dinesh. It is – he’s someone that I have e-mailed with for a very long time, but I only met earlier this year because he kept his identity hidden, for understandable reasons, when we first – when we first started talking about some of the issues that Ranbaxy was having.

But, more broadly, India’s pharmaceutical industry is an absolute phenomenon these days. Over $4 billion worth of exported drugs to the United States, growth rate of 25, 30 percent a year, and that rate of increase of supply of pharmaceuticals to the United States and other parts of the world is it looks like being sustained at some level by double-digit growth.

From the inception of the Indian drug industry, it has always set itself apart from Western competitors, often too much Western consternation, in its history of ignoring patent products within the Indian system. And that changed just over a decade ago, when India joined up to the TRIPS agreement of the World Trade Organization introducing and protecting product patents. Much has been written about patents and India’s adherence to them. That is not the topic of today’s discussion. And that’s the last I’m going to mention of it.

In an unbelievably positive light, India’s contribution to pharmaceutical production is undeniable. It is – it has increased access to – for millions and millions of people around the world. It has made myriad medicines at unbelievably low prices. It’s – this is, you know, manifestly obvious in HIV programs that the US government supports, but it’s also true in nearly every field imaginable. In my research team samplings of medicines in emerging markets, in 22 cities in emerging markets, well over a third of those products came from India.

In the last decade, stories of falsified and substandard medicines have accelerated. From our samplings, again, we identified falsified products, substandard products – that
is those products made by legal manufacturers, which were simply not good enough – falsified products being made often by criminal entities, sometimes by legitimate companies that, if you like, are cannibalizing their own brands, and then degraded medicines. And there are no hard and fast truths when it comes to where the problems are. But we did find a strong correlation with poor quality medicines with poverty and illiteracy. It is a far from perfect correlation. There are some very poor countries with better performance in this area and there are others which – such as in middle-income countries that often do quite badly.

Those succeeding in combating poor quality medicines and ensuring high-quality medicines do so because of a concerted effort to combat the poor drugs in the market and ensure good quality drugs in the market. Everyone loves to blame foreigners when poor quality drugs are being discussed, but every country has its own problems with homegrown criminals and often homegrown production of poor quality products.

But there is an undeniable aspect to the pharmaceutical industry, which is, over the last 20 to 30 years, the business has gone truly global. And there are potentially far larger problems, especially with ingredient oversight from around the world going into the production of medicines.

While there are problems with falsified, often known as counterfeit, medicines made by criminal enterprises, our main focus today is not on such medicines but on medicines which are substandard in most people’s definitions of that word. In other words, they’re not performing as expected but they are made by legal manufacturers.

And some of the studies my colleagues have done, sometimes you see there’s these gross errors. There would be incorrect active ingredients, the stuff that’s supposed to help, help treat your disease or condition. Sometimes the errors would be in having the right ingredients but in the wrong amounts. Sometimes there would be the right amounts and the right ingredients but they would be poorly formulated so there would be major problems with solubility so the drugs wouldn’t be available.

But sometimes the errors are hard to spot and the drug simply doesn’t work but it’s – and it’s not bio-available, in the jargon, into the patient but they’re hard to notice. In some what are known in the jargon as narrow therapeutic index conditions or diseases, so, for example, for transplantation, for anti-depressants, for some fields of oncology and other categories impurities, for example, undermine the efficacy of products, but they’re very hard to identify in advance. And they need to be built into the systems of production to ensure that those low-quality products do not make it onto the market.

Of course, all manufacturers have problems with production. It doesn’t matter where in the world you are, producers have problems. How they respond and how the regulators overseeing them respond often dictates our trust in those products overtime. And this is why we started to look at India.
It is producing an amazing array of products very cheaply, as we’ve already said. But earlier this year, for example, we started to see what I would consider a smoking gun. You start to see production of products – for example, there was a study done by the Food and Drug Authority in Ghana along with the US Pharmacopeia and United States Agency for National Development that showed that about 95 percent of the maternal health products – Ergometrine, Oxytocin, which is used to reduce the risk of post-partum hemorrhage, after mothers have obviously have just given birth, we found that 95 percent of the products didn’t work very well. These appeared to be by legal manufacturers, a lot of them from India and China.

The regulator in India, the CDSCO, has been routinely criticized by various different Indian parliamentary committees, calling it corrupt and colluding with local and foreign companies.

And then, of course, there is the decade-long problem at one of its famous companies, Ranbaxy. And I think most worrying of all, and I think why, you know, I’m most interested in this topic is that the problem we’re exposed by a whistleblower, who we’ll get onto in a second, but exposed not by Indian domestic agencies but by the US Food and Drug Administration.

That leads me to the question of how safe are Indian products. Can we trust the Indian regulator to do its job? To help us understand this specific issue of Indian drug quality and drug quality oversight, I’m delighted to introduce our main speaker today, Dinesh Thakur, the man responsible for blowing the whistle on the problems at Ranbaxy.

As I mentioned before, once he’s spoken, we will have remarks paid, two divergent and impressive experts: Andreas Seiter is the World Bank’s leading medicines expert who can put India’s unique contribution to medicine production, good and bad, into context, and Harry Lever, who, as I’ve mentioned already, is a leading cardiologist at the Cleveland Clinic, who works at the sharp end, as it were, and who has his own concerns about medicine quality in the United States.

Welcome one and all. Thank you very much for making it here on a Monday after Thanksgiving. It was the only day that we could do so thank you for coming out on – I realize a lot of people have been traveling back, even travelled in this morning. I know that when I came to D.C. last night, the train station was mayhem. I’m sure it still was this morning.

And I know there are a lot of people who couldn’t be here so I’m going to look into the camera, which I believe is up there – a lot of people. I’ve had well over dozen e-mails which probably means a lot more people didn’t reply I know are probably watching this so thank you for joining us via the Internet.

If you have questions for the panelists – we’ll obviously take questions from the floor after our speakers have spoken. If you have questions to the panelists and you’re watching online, e-mail me at rbate@aei.org. And I will be routinely checking my e-mail.
I won’t be checking, you know – I won’t be checking my other e-mails, I assure you. But that means that I can ask your insightful questions to our panelists.

But for now, that’s my introduction over. And I will hand over to Dinesh Thakur. Dinesh.

DINESH THAKUR: Thank you. Thanks, Roger. And thank you all for taking the time to come and participate today. Roger asked me to come and talk a little bit about my experience, what had happened at Ranbaxy. And I think, you know, more importantly I think the larger question, not so much as what actually happened there, because it’s been very well written by Katherine (sp) and other journalists here, I think the larger question is, what does it mean for us going forward? I think that’s where we need to focus on.

This is a presentation that’s on the screen here. Let me draw your attention to that. This was a presentation made by the head of pre-qualifications at WHO in 2007. And I’m not going to go through all of it. I think it’s instructive to look at one or two slides in here because this information is public. I did not ask for WHO’s permission. This was available publicly so I got a copy of it.

But it’s interesting to sort of look at a couple of things in here to try and understand the extent of the problem because what gets reported and what actually gets understood, acknowledged, is in my opinion the tip of the iceberg. There is a significantly larger issue that we have that we’re dealing with. And way back in 2005 or 2007, it was very well known but it is only now that we’re beginning to try and talk about it and try and understand what really is going on. So I’m going to skip through all of these because this is not relevant to what we’re talking about.

What I would like to draw your attention to is this particular slide. So this was a WHO pre-qualification inspection done at an Indian contract research organization called Vimta Labs. You can see up there, it says the name of the CRO. It tells you where it was located. And the last box that you see at the bottom, it talks about the study that they were doing. It talks about the fact that this is an antiretroviral, Lamivudine. And it tells you who the study was being done for. And it talks about the protocol for the particular study.

So these are observations that were made by a WHO inspector and they were acknowledged in a public forum in Cairo, in 2007. So let me just get to – I mean, these are some of the observations, OK? So, by itself, they’re actually very, very scathing, but let me get to the point which I wanted to sort of start off with, which is here.

As you know, for genetic drugs, the primary rationale for getting approval is you have to prove that the generic version actually is what’s called bioequivalent to the brand manufactured drug, right? And the way that you prove that is typically by giving patients both drugs, the branded drug and the formulation that you want to get approved. And you want to compare how it gets metabolized within the patient and try and understand, you know, how long does it take for the drug to actually get into the body, how long does it
take for it to clear the body, understand exactly what the concentrations are in the blood level in order for that to be effective.

These observations are – if you can just read those, it says, no study or protocol number on ECGs – those are essentially heart rate monitors – to link them to the study. Out of 95 such – of the 95 copied by the inspectors, 43 appear to have no record from one subject; 21 from the second subject, and 11 from the third subject. So out of 75 electrocardiograms that they reviewed, they came from three people. What does it tell you? This was known in 2000.

So if I go back here, this inspection was done as part of pre-approval in 2004-2005. What does this tell you? Do you have the confidence that the drugs that you’re taking now are essentially what they’re supposed to be? And that is the reason why I did what I did and what culminated in the events that have been reported in May of this year. I think the problem is much bigger from what we understand.

See, the challenge is that if you are taking an antibiotic, if you have a fever, if you have an infection and the drug doesn’t work, you know within a day or two the drug doesn’t work. The fever doesn’t come down. But if you have – if you’ve been prescribed a statin, you know, to control, you know, an outcome that may or may not happen to you, years down the road and the drug doesn’t work, how do you measure whether the drug actually works or not? Do we understand how to sort of look at what that particular drug is doing within the physiology?

And that I think – so, this one particular slide – and there’s more here. And this presentation is available publicly so I’m sure you can Google it – the challenge is that we have this problem right now where 80 percent of our prescriptions in the United States today, you know, are generic prescriptions. They are dispensed, you know, for cost reasons. Drugs that are made – you know, that are the copies of brand drugs. And the majority of these drugs essentially are either manufactured wholly or have ingredients that come from outside of the United States.

So the question is how big is this problem, what is the impact on public health, and what are you going to do to try and address it, right? So we see that the things that are happening right now, the FDASIA, you know, regulation that came into being, the talks about additional hands in terms of inspectors is – you know, obviously, is a great first step. Clearly, it is implementing that. There are more people in India and China right now looking at compliance to try and address, you know, some – so that you won’t have issues like this come up.

There are issues around drug shortages so I don’t know if you knew this, but when the FDA actually invoked the application integrity policy in Ranbaxy in 2008, they left off one particular drug that was manufactured by this company that was still allowed to come into the country, valacyclovir because that was the only manufacturer that was making that particular drug. So clearly, the (FDA ?) acknowledges that they understand that there is a need for us to have more comprehensive policy in terms of where we get
our drugs. And if there’s only one manufacturer, how do you ensure that the drug continues to be available for patients who actually need it, right?

So those things are happening. The larger issue that we have right now is that there is a disconnect between the policy of what we see among regulators who are trying to have a consistent framework around what we need to do to ensure public health across many different countries and a very sort of intransigent and obstinate policy regime and regulator that we see in India.

How do you sort of – you know, I mean, you’re not going to get away from not sourcing from India and China. That train has left the building. I mean, we used to manufacture all this – the drugs in Puerto Rico, you know, when I used to work for a large pharma company. You know, all our manufactured drugs came from Puerto Rico. Now they come from India, and China, and Latin America. The drug supply chain has become global. Whether we like it or not, this is how it is. The question is, what are we going to do to ensure that the stuff that we put in our bodies is what is supposed to be? And that is a question that hopefully we’ll get a chance to talk and answer.

MR. BATE: Just to put things in perspective, I mentioned in my introductory remarks, every company has problems. It doesn’t matter where they are in the world, they will have problems in production. What makes – what makes the – I’m not saying it would be unique, but what makes the problems in India more significant for the global supply of pharmaceuticals as opposed to Puerto Rico? If indeed you think it does, because I think for a lot of people, it’s not necessary – who may not have spent time in India, it’s difficult to understand why this may be – may be an issue.

MR. THAKUR: Well, I think, you know, we sort of (address ?) off it, what you said in terms, you know, your ability to control. There was a time when, you know, in order for the FDA to enforce the same level of inspections – I mean, the two aspects of drug quality, right, one is policy, which is prescriptive, how do you do it; the other one is compliance, which is whether you’ve done it and making sure that you’ve done it properly.

In order to try and enforce the compliance aspect of it, there was a time not that far ago when regulators needed reasons to go into India or China. I mean, heparin was a clear example, what you saw with Baxter in China, right, manufacturer of heparin. And there were actually deaths related to that. And inspectors – (inaudible) – actually go inspect their – you know, the ingredients for heparin were actually being made. So as a consequence of that, things have changed. FDASIA regulation now talks about inspectors being on the ground.

So the question that you’re asking is, why is it more important, you know, in the context of India? For two reasons: I think that, you know, by and large, Indian generic manufacturing industry has supplied low-cost and effective medication through the world. And there’s no denying to this fact that – you know, there are companies who do the right thing. But if you don’t have the same statutory inspection piece in place, your
ability to take liberties to try and address, you know, the monetary gain when you have, first to file that makes $600 million is too huge. It’s too big. And in those cases, you know, when you have the compliance aspect of it that enforces, you know, the regulations debate ought to be, without having to worry about, you know, inspectors asking for visas, giving notices ahead of time, which doesn’t happen in the United States. I mean, FDA can knock on your door anytime, and say, well, we’re here to inspect – you know, the – (inaudible) – inspections or just systems-based inspections. It didn’t happen that in India.

MR. BATE: But I assume the Indian regulators have the ability, not only visas, to be able to go in and inspect. I mean, maybe you could just briefly just tease out the difference, because from my understanding, drug quality is overseen from the center, by the CDSCO but the drug manufacturing is overseen by the individual states. So is that disconnect – does that create a problem?

MR. THAKUR: Yes. It does because, you see, unlike in the United States, drug regulations in India are sort of – you know, they’re disjointed so the national regulator essentially is responsible for overall policy but the individual states oversee compliance in quality where the manufacturing plants are located. So, clearly, their incentives are not alike. States make revenue from licensing but they don’t necessarily have anything to say about the overall quality of the drug, which is – (inaudible) – to the national regulator.

So there are issues within the way the regulation is actually set up and the systems are set up of governance in India so that, you know, they don’t sort of align themselves to have good public health policy. And that needs to change. Clearly, it needs to change. The Indian equivalent of an FDA commissioner reports to an undersecretary within the governance structure so, clearly, it doesn’t have the level of visibility or the influence that is needed for sound public policy in India. That needs to change. The budget of the country for over a billion people was $7 million for public health until about two years ago. I mean, are you surprised that, in effect, they’re doing what they’re doing then?

So, clearly, I think, you know, Roger was talking earlier, this morning, that when it comes to India, issues about patent actually get, you know, highlighted at a very high level, at Kerry, and Biden, and the congressional level, but when you talk about regulation, it’s down in the weeds. And so you really get the attention that you really need in order to address some of these systemic problems. And so there’s a dichotomy there, right? A part of what I think Roger is trying to do is to try and draw attention to the fact that this problem is big and it needs to be discussed at a different level than, you know, where it is discussed at the moment.

MR. BATE: One final question before I bring Andreas in. The implication of what you’re – sorry – the outcome of the implication of what you’re saying is that you end up with kind of different sets of standards based on the market that you’re exporting to so that, in principle, you might be selling good quality products to the United States but poorer quality products to other markets in the world.
Is that – do you see that as something that is widespread across Indian industry or is it just – it’s just the stories that I’ve read about? I mean, in other words, do you think this is a measurement issue? You know, one of the things – whenever you’re dealing with sampling of – where there’s a paucity of data, you wonder whether you’re looking at a systemic problem or it’s just that this is what’s been reported? Do you think it’s systemic or is this just isolated?

MR. THAKUR: No. I believe it is systemic because it’s the way that the market has evolved. You see, there are a set of companies that actually import – that export to Western markets, whether it’s the United States or Western Europe, that essentially comply with a different set of standards that are applicable to the local markets here. I mean, to the extent that they’re manufacturing plants that are dedicated to essentially supply to the Western markets.

Why is it that a company like Ranbaxy has, you know, nine or 10 manufacturing locations in India and only two of those supply to the United States? That’s by design because the people that work there, the processes and systems that are employed at that particular local conform to what the FDA requires, and they are different, completely different from other manufacturing locations that supply to the local market that supplies to Africa and Latin America where the regulations are perhaps not as stringent as there are in the United States. So this is a systemic issue. This is not an isolated incident.

MR. BATE: The last follow-on question. Do we see evidence of an impact of that yet?

MR. THAKUR: Well, I mean, see, this is the hard part. I like in the United States where there are good systems where you can measure the outcome. For example, in safety, you have the – (inaudible) – system in the United States where, you know, data is actually collected in a very, very, you know, effective manner. Those systems don’t exist in India. Systems of governance don’t exist. So how do you sort of prove that there is actually harm in public health if you don’t have proper systems in place to measure?

MR. BATE: I don’t know. Well, on that note, I’m going to – I’m going to hand over to Andreas to maybe sort of respond to some of these comments and give his perspective from your vast travels around the world where you see the good, the bad, the ugly, and everything else from the pharmaceutical production.

ANDREAS SEITER: Yeah. And you may have to stop me because I just recently traveling and I have some new anecdotes to share.

So, first, I would like to thank Roger in particular and others here in the room for actually keeping the finger in the – in the – (inaudible) – you know, and stirring, and creating pain, and advocating for, you know, taking this subject seriously. My gut feeling – and I have no proof of that – is that it’s actually getting worse. Maybe it has to get worse before it can get better when, you know, everybody takes attention and more significant resources focused on the solutions.
But it appears to me that this whole business of drug counterfeiting or serving markets that are not particularly sophisticated, with lower equality products from the industry side, and that includes the legitimate industry, a company like Ranbaxy and others, up to the totally criminal organized crime related, and there are some interesting things in between.

One country in Europe, where I just came from, a few weeks ago, they arrested some high-level people in their regulatory agency together with a professor of the school of pharmacy because it was discovered that this guy was running an illegal drug manufacturing place, and they even had the customs stickers that have three security features. They had their own manufacturing for the custom stickers and they were making drugs that are legally in the country but in a fake version, you know. And that’s a small country. So you wonder, you know, if they had that sophistication, you know, how—and I have other stories of other countries that are not India that are—European countries are involved, Central Asian countries involved, Latin American countries. So it’s not all focused on India only.

But, of course, India is very dear to our heart as public health people because, as Roger pointed out, it’s the source of so many affordable essential medicines that are needed everywhere for our programs. I mean, we, the World Bank, we are financing health systems strengthening in many countries. That means basically we are helping governments to improve their health systems, focus on primary care. Often mother and child health at the moment is a big topic. There are programs that create certain financial incentives, for example, for nurses and midwives and so on to do the right thing in order to save the life of mothers and children. And all that needs medicines.

And, like Roger pointed out, if the drug that you used to stop bleeding, which is the cause of death for many mothers, if it doesn’t work, then the mother still dies, although you have strengthened the system, but that final piece that you need in order to have the effect fails you and everything is basically wasted. So that worries us as an institution and many of my colleagues very much. And I think that’s why we have in our institution a strong support for putting more focus also on regulatory strengthening and regulatory systems. And that’s a long way to go.

I mean, I was in India some years ago because we had actually—in the early 2000s we had a project there for strengthening the regulatory authorities in several states and in the centers I think, the building in which the central authority is, is actually financed by a World Bank loan. And I was the one who had to evaluate the project after the fact. And it wasn’t too good a picture. You could see there were some states that are better and other states that are worse. And those that are better, they made better use of the money and those that are worse, you see simply no capacity to even absorb funds. There’s a bureaucracy which is very kind of—how should you say—it blocks, you know, every layer it has blockages so the people in the lab, they know what equipment they need but they can’t get it although the money sits somewhere at a higher level because the communication, the decision making doesn’t function.
I was at a workshop for two days with drug inspectors from different states. I was completely impressed how technically competent these people are, but when you talk to them privately, they say, yeah, we see all the problems in these factories and we report them but nothing happens because it’s the political level where the interest is more in maintaining this facility, maintaining the jobs, the tax income, maybe the bribes – we don’t know, yeah – and if there is damage done to poor people in Africa, who cares?

I mean, that’s frankly – and we shouldn’t single out the Indians for that. I mean, cheating poor people in order to make money is something that also has happened in this country and hasn’t led to anyone being in prison yet when you think of the financial industry. So it’s really nothing to feel morally superior but just accept as a fact that whenever you have an industry where as a consumer I cannot judge the quality of your product like I can with my cell phone, we need a competent regulator and we need transparency all down the chain. And we don’t have that in these global supply chains right now.

So I think we have a number of technical people. I mean, Lambert (sp), whose presentation was here on this screen is one of the stars in the international community in this field. We are meeting from time to time. We are getting better. We’re having now some funding to strengthen regulatory agencies in Africa. But this is a project that can take a decade and longer, as you know, when you think – look back at the history of the FDA, the history of the European agencies. It’s not happening over night and it needs a the constant reminder from, you know, the advocacy people and from media and so on to – you know, to keep the topic somewhere in at least, you know, page three if not once in a while the front page and wake up the policymakers that this is an important subject. So, I mean, this is where I stop and then we can –

MR. BATE: Well, thank you. I’m always happy to be a pain in the ass. That’s my job. That’s my – you know, unwritten definition of my job here at AEI.

One of the things that I see as being crucially important about India and why the focus on India is that it does – if for all of those good reasons, that it is part and parcel of the – you know, U.N. AIDS programs, the World Bank, is because of, generally speaking, good quality products at low price. That’s the impression and to a large extent, that’s true.

But India is also – when, you know, antibiotics were first introduced in the West – (inaudible) – antibiotics and antibiotic resistance, a lot of the problems of poor public health had already been solved. There was good sanitation. There was relatively good hygiene and good water quality. India is not unique but it is across South Asia as well, as a whole, you’re often dealing with emerging markets with poor sanitation, hygiene and water quality and very low drugs costs, which means that the demand is increasing. Especially as people in India and South Asia get wealthier, the demand for these products is greater than any other part of the world because the level of infections are much higher.
So that’s one of the reasons – I mean, there are a lot of reasons to be interested in, for example, the products that make it into the United States. And I particularly say that for the media in the United States that, you know, by its very nature is less interested in, you know, in other parts of the world. But it strikes me that there are risks – and I don’t want to bash the drum of New Delhi beating the long-term resistant Klebsiella pneumonia because – you know, it’s called New Delhi because that’s where it was first isolated but this happens in parts of the world but I’m wondering if we’re going to start to see more issues of drug resistance because of those unique circumstances in India and why the Indian drug industry is so unbelievably important, but it’s in a market where more and more people are accessing medicines, which is good news, but if the quality isn’t good, you’re actually just going to be ramping up resistance. Or am I being a Western alarmist when it comes to that? You can both answer.

MR. SEITER: I don’t know. I don’t really know enough about the science of resistance development and whether it is about, you know, the breadth of covering a population with overuse of antibiotics and whether the quality differences have an impact on that, whether they are in terms of how big does it have to be the quality difference in order to lead to an under dosage of a patient who actually carries bacteria, because often you treat viral infections. And if I treat a viral infection, I may not contribute much to the resistance of a pathogenic bacteria because it’s not present in the patient.

I mean, as I said, we have – I think at the Center for Global Development here they have people who are more competent on antibiotic resistance development. My prejudice that it’s the more critical part is for in-patient, for hospital treatment where you get the multi-resistant drugs, and then, of course, you have the specifics like MDR-TB, no, the multidrug-resistant tuberculosis, which is particularly big in India. And that’s actually an area that, again, this is kind of home to me because we are just preparing another project in India where we want to finance the government for the purpose of ramping up their provision of MDR-TB treatment, which, again, raises the issue, how do we secure through their procurement that they buy quality products, no? So we are – you know, we’re moving in a loop here because that is really one of the issues where you don’t want to have any margin of error if you’re treating people who are already at the edge of being treatable at all.

MR. BATE: I think you make – you know, make a very good point. I mean, drug resistance occurs everywhere and it is primarily from overprescribing and everything else. I just wondered if you saw this as being a contributing fact. We can come back to that because I think the MDR-TB stuff is very important.

I’m hoping now – I’m looking at myself which is not what I wanted to do. I’m hoping now that Harry can join us. Harry, can you hear us? There he is.

HARRY LEVER: Yeah.

MR. BATE: You look great, Harry.
MR. LEVER: Thank you.

MR. BATE: Can we hear – speak into the –

MR. LEVER: Can you hear me? Can you hear me?

MR. BATE: Yes, we can. We’ll all be quiet so we can hear you very well. So please join in the discussion.

MR. LEVER: Well, sitting here as a cardiologist at the Cleveland Clinic, I’ve noticed that some patients, when they come in to see me not doing well, and particularly in heart failure or the disease I deal with, hypertrophic cardiomyopathy, which is an abnormal thickening of the muscle, particularly with heart failure patients, I have noticed that there are some drugs that they take that they seem not to be effective.

For instance, Furosemide, which I’ve – because of the articles about Ranbaxy, I became more cognizant of, noticed that if a patient would come into my office with symptoms of heart failure that if I just switch the manufacturer from Ranbaxy to another one, still could be generic, and gave them the same dose, they got a very good response.

And that always troubles me because what I don’t understand is – and maybe Dinesh could explain it – is that it’s not like – it must be that every tablet isn’t bad because we see people on these drugs, and they’re not all falling off with heart failure, but some of the patients that come to see me, I’ve noticed, that they don’t – aren’t doing well, and when I switch them, they’re better. Is it that the batch-to-batch consistency is a problem or, you know, what can we feel is the – you know, the consistency of the drugs being made? That’s where I think there’s a problem. And maybe some drug companies are more consistent in making consistent drugs, but maybe companies like Ranbaxy aren’t, that they still put the active ingredients, but, for some reason, it’s not – it’s consistent.

MR. BATE: We’ll get onto the drug quality issues in a minute from this side, but perhaps for the audience and also for myself you can explain to us the – if that’s the right word, the clinical impact of being on a poor version of Furosemide, for example.

MR. LEVER: Well, I have one patient who called me and told me that he was short of breath. He’d go to bed at night and he was – he’d wake up short of breath and found that he was on Ranbaxy’s preparation – it was 80 milligrams of it. And so what we did the first night was – until we could adjust manufacturer, we gave him a double dose. And he felt a little bit better, but over the – then we changed the manufacturer, keeping the dose the same, and he lost 15 pounds of fluid over the next week. And from that, he felt better.

MR. BATE: Furosemide is a diuretic so you should be losing water.
MR. LEVER: Right. And he suddenly just – nothing else was changed. We kept the dose the same and he lost – he lost the fluid, and he felt much better, and has had no recurrence of it. And this is more than a year now that that happened. There were no other – you know, no other reasons to think that his heart had suddenly worsened or anything of that sort. And, you know, I – again, it was striking to me that, you know, he got better so quickly.

So, again, the question is, is it just lack of consistency, you know, because if you treat a patient with heart failure – if a few tablets don’t work well, then they start accumulating fluid, and then, you know, it just may become a vicious cycle. It may not be that every tablet in the bottle is bad or is it that the whole batch is bad? I mean, I have not been able to figure out when we say that these companies have problems, what is it – is the problem?

You know, is it that – you know, we in this country over the years had always known that batch to batch consistency was extraordinarily important and there was as drug that’s an old drug, that Digoxin, that we used to treat heart failure. And years ago, we knew that there was one manufacturer in this country who could make it consistent. It was a very hard drug to make consistent. And we always would write that – for that particular manufacturer name brand because we were all taught that was consistent. The same was with nitroglycerin. It had – that was made by Park-Davis. They knew how to make it. And we didn’t have a problem, but when there were other manufactures, the drug didn’t work as well, formulation problems or whatever.

But now, you know, I guess I would have thought that there were certain rules when you make drugs that when they come out of the machine, they should all be the same. I guess that’s the question. Why is there this seaming inconsistency?

MR. BATE: And before we get on to the answers to those or Dinesh’s response if not perfect answers to them, you’re not just seeing this with Ranbaxy products, obviously.

MR. LEVER: No. No.

MR. BATE: Are you seeing this as an increasing problem? I mean, has the situation changed in the last decade for you?

MR. LEVER: I would say yes. And I would say it’s not just on drugs coming into this country. We have had issues of drug quality in this country, with drug manufacturing in this country as well. It’s not just overseas. I mean, it’s sort as if there’s an illness in the drug industry where the quality isn’t quite as good as it was before.

I mean, in general, things are pretty good. But you come across these times where there have been a lot of recalls that were things we have never heard about. In 2009, there were 1,740 drug recalls, an outstanding number. You know, if you’re making drugs, you don’t want to have them recalled. You want to make sure that they’re working right. But
to have that number of recalls, you being to wonder, what’s wrong with an industry where those things happen.

And then, we have this horrible problem in this country of drug shortages, chemotherapy drugs, antibiotics. Even a simple drug like epinephrine, we had in short supply in our hospital because of manufacturing issues. And you say, well, epinephrine, every – you know, that shouldn’t be a problem. That’s an old drug we use in acute cardiac emergencies and on every crash cart in the hospital. How could we have a problem with that? Let me tell you, we had a problem with it. And so it’s not just confined to overseas. It’s in this country as well.

MR. BATE: The final point I’d like to make before I let Dinesh answer is that I shared with some reporters earlier and we’ve been handing out – I believe it was in the packets. If not, I’ll add to it – the poster by Preston Mason from Harvard Medical School, which showed 36 generic formulation of Atorvastatin, which is Lipitor, which had impurities which are undermining the performance of the drug. The samples were taken from the United States, Europe, and across Asia.

You were the one who put me on to this. I was wondering if you could explain the significance of having Atorvastatin at least in vitro it looks as though it has dubious performance based on impurities, because as I was mentioning earlier, and I think we’re beginning to see in the literature for antipsychotics, antidepressants, oncology products and transplant products, the narrow therapeutic index products where there are problems with impurities, do you think this is now an issue for statins?

MR. LEVER: Well, I’ve had some patients. One patient who was on Atorvastatin, again, from Ranbaxy, right about that time, when there was this talk of these glass shavings in the tablets, and he came in to see me, and his cholesterol was 100 points above what it was. And all I did was kept the dose the same, called the pharmacy and said, give him the name brand. And we checked it within a month and it was back to normal.

And I had another – I had another patient with a different drug. She could not tolerate Atorvastatin. She was placed on Pravachol, from actually another Indian drug company. Her cholesterol went up and all I did again was change the manufacturer, kept the dose the same and the cholesterol dropped and it’s been normal – this is now more than a year. It’s remained normal.

So, you know, when you’re giving somebody – actually, statins are relatively easy because you can measure something. You can see what the level is, whereas with others, it’s not so easy. And, you know, when you’re treating a heart failure patient, do you know, is it really the diuretic that’s a problem or did they cheat on their salt, or did something else happen? You know, did they drink a little extra alcohol? You know, it’s so multi-factorial that it’s hard to isolate it. And that’s why I’ve tried, if I feel that there might be a problem, I just change the manufacturer and keep the dose the same so that I
try to eliminate one problem. But, you know, there are all kind of – heart failures are a
difficult thing to treat.

And, you know, and we’re worried – in this country now, we get penalized if we
have readmissions to the hospital within 30 days because people come back with heart
failure. Now, is it because they got the wrong drug? Is it because they weren’t taking
their drugs? Is it because they were eating wrong? It’s all complicated. But the one
unknown that we can’t stand for is to have a drug of poor quality or inconsistent quality. I
think data is like an algebraic equation. You know, you have to have – you’ve got to
eliminate the unknowns, and we would always hope that the drug manufacturers could
eliminate those unknowns for us.

MR. BATE: Harry, that’s very informative and worrying. I would be interested,
Dinesh, in your response to a lot of the points that Harry raised about differences between
batches or within batches, because a lot of these products probably – you know, the
manufacturer overseas has got approval. So maybe you can touch on two things: the in-
batch change and then the fact that our assumption is that if it’s approved by the FDA,
knows how to make the product. So maybe you can address those kinds of questions.

MR. THAKUR: And this is really very enlightening, Harry. Thank you. That was
– those anecdotes that you actually, you know, recounted, sort of take me back to the
time that I used to work for – you know, for Ranbaxy.

But here’s the thing, right, so how often does the data about you switching
different generics from one generic to another generic actually get reported or get
consolidated, because in order for us to sort of look at effectively, you know, what the
impact is of this poor quality generics, it’s important to sort of understand how many
times it does happen, because – I mean, clearly, you’re doing the right thing for your
patients, but how – as a country, from a public health point, how do we consolidate that
data and how do we look at it to see how many times does it actually happen and what
are we going to do about it, right? So that’s – I mean, it’s a rhetorical question. I don’t
know the answer to that. Perhaps you would be able to sort of, you know, help answer
that as we move along. But what you’re seeing is – it doesn’t surprise me.

So let me tell you of one particular product that required (oxygenation ?). So
when you make the chemical, the chemical process requires a step that – you know, it’s
called oxygenation, so it’s essential adding a little oxygen molecule to the drug. The
reason this was important was because if you did the oxygenation correctly, the yield
would be 99 percent. If you missed the oxygenation step being done properly, you’d get a
90, 90 percent yield.

And what companies that don’t have the sort of – I shouldn’t say fear, but their
own worry about, you know, an inspector coming up and showing up at your door
uninvited, at any moment’s notice, they would blend those two batches and essentially
come up with an API that would have a 95 percent yield. And in some patients, if you’re
looking at a narrow therapeutic drug, indexed drugs, it would make a huge difference. I
mean, if you’re using a diuretic, clearly, water retention becomes an issue at that point in time. So batch-to-batch variability I think is a critical aspect of it.

What had happened in countries like India, because of, you know, poor local regulations and the fact that the FDA needed visas to actually go visit this manufacturing locations in the past, manufacturers took, you know, sort of liberties in essentially blending good API, API that would actually pass and then get the right kind of yield with poor API that should never actually make it to the drug. They would blend it together and then make formulation out of it. And guess what? You’re the receiving end of this particular process.

So the point here is that, you now, with FDASIA right now and inspectors locally located within the country, hopefully, you won’t see these things going forward, but the problem is real. The problem is real but I don’t know how big the problem is. Until we have the data that actually helps us define how often does this really happen, it’s kind of difficult to get our arms around it.

MR. BATE: Harry, did you want to respond to Dinesh’s question?

MR. LEVER: Well, one of the things we’re thinking about doing here is looking at our readmissions for our 30-days readmissions to the hospital and trying to figure out what were these people taking. Does that have a role to play? I don’t know that it does. I mean, because I still have this nagging question, everybody’s not getting into trouble. It’s not like everybody’s falling off the – you know, falling off with heart failure. But it seems like there’s a higher incidence of it, you know, when you deal with some of these manufacturers.

I mean, I had another woman who had a striking response when I changed – she was on two drugs. She came in with what we call hypertrophic non-obstructive cardiomyopathy, a thickening of her heart muscle where there’s no obstruction to the blood flow out of the heart, and I had been following her for a number of years and she was perfectly stable. And this one day, she comes in with not fluid in her lungs but just really severe shortness of breath.

Nowadays, there’s a blood test we can do called a brain natriuretic peptide which gives us an objective measurement of how bad the heart failure might be. And the upper limit of normal is 125. Hers was 4,100. And so all I did was switch, again, the manufacturers, made one additional change. I gave her the same drug but a little more sustained release than she was on. That’s all I did. But, basically, the doses were the same, and the level dropped to 700 within a matter of a couple of weeks. Her exercise time increased and she continues to feel better. And so – and both of these drugs were from two separate manufacturers in India, not Ranbaxy; two others we don’t have to mention, but they were – they were – she got better.

And, you know, the other drug that I have a lot of trouble with and have had a lot of experience with is Metoprolol Succinate. It’s a sustained release Metoprolol that the
problem seems to be that the release mechanism is patented different than the drug. And so, when a drug goes generic, the release mechanisms are different. And we’ve had numbers of problems with that drug, American-made and Indian-made, where the patients clearly don’t do well. And all I do, again, is switch the manufacturer, keep the dose the same, and they seem to get better. Not everybody, but a large number of those patients seem to feel better.

And I think one of the concerns I also have about pharmacology is sustained release drugs, because how can we be sure that one manufacturer to the next is coming up with the same release mechanism that will give us the same results? And I think that whole issue has not been well addressed with our regulators in our country as well, because we just had a drug, Budeprion, that the FDA published a paper a year ago in the “New England Journal of Medicine” where they showed that the sustained release generic was clearly not the same as the sustained release name brand. And the drug would – the generic would release too early in the day so that the depressed patient wouldn’t have that effect later in the day.

And I think that that whole issue needs to be looked at as well, as, you know, these are newer kind of drugs with these sustained release mechanisms, you know. And that’s a – that adds a whole other problem here. But that – you know, we start making these drugs overseas, how are we going to know how those pharmaceutical companies are making their release mechanism?

MR. BATE: All very, very interesting points. One of the things I wanted to go back to Dinesh for is that I mentioned in my introductory remarks that action against Ranbaxy from your information was taken by the FDA. How has that action been viewed in India?

And I ask that question, one, because I’m interested in the direct answer but also because, you know, India and the United States, India and Western Europe have had, you know, lots of battles over patents over the last 20 years. I’m not interested in that. But what is important about that, it has created distrust on both sides. And it has created, if you like, a kind of – for want of a better word, a fortress approach, in other words, whenever there’s a complaint, it’s, oh, you would just say that because.

So I’m wondering what the response was and also whether you see that not only because of all the other stuff we’ve already talked about, but India is in a unique position because it’s been in battles with the West for 20 years on these topics.

MR. THAKUR: As you said, I think that, you know, that the decks are loaded, you know, on both sides. So any conversation has always looked through this colored lens of the West trying to sort of take away the dominance of the Indian generic pharmaceutical industry, which, you know, I think there may be some truth to it, but I think that, you know, in this particular case, we’re talking about something completely different. But, unfortunately, the conversation gets tainted with that particular aspect of it.
Coming to the question that you asked, which is, what has the response been, I mean, I only know from news reports because, you know, I have no direct knowledge – nobody’s contacted me to ask me what did I know, how – you know, how did I respond to something like this.

There’s something that I learned from the newspaper reports that the Indian regulators sent inspectors into the same facilities that are still under import banning from the United States and they haven’t found anything wrong. That’s a data point.

In the media, the conversation has focused around the fact that somehow, the definition of what constitutes quality within India and the United States is very different. Indian standards and Indian definition of what constitutes quality of a drug is somehow different than how Western markets perceive it and this was merely a violation of documentations on how – (inaudible) – Ranbaxy was held accountable for it, which in my opinion, you know, is completely baloney but that’s the conversation. That’s the response.

MR. SEITER: Also, I can relate to that. I mean, in our conversation sometimes with decisions makers, it also – so quality, bad quality would be that you will find actually that somebody dies from taking the drug. So as long as nothing happens, the quality has to be OK. Unfortunately, this kind of layman’s view is relatively widespread. I mean, I’m again not talking specifically about India.

What I find interesting also it comes up in these like anecdotal stories of individual patients where can be a million reasons why these patients fail and then switching to another drug are getting better, which have nothing to do with the drug as has been certainly – I was in my earlier life also running a ward with, you know, chronic patients. I’m familiar with this revolving door, heart failure, and so on. But it’s still – I think what it really points to is that this ongoing reporting about scandals is doing something to the reputation of the products made in India.

And that’s a point that I can also observe in Africa, in our client countries, where they have been shaken repeatedly by rogue Indian companies getting into their markets with bad quality products that even they, with their own limited regulatory capacity, can identify.

And just when you go on the Internet and you search Ghana FDA, you will find some reports about a company called TOBINCO, which has been active in Ghana, has been registered a handful of drugs, and then selling all their drugs or many of them without registration in the market because the FDA is not really able to control everything that is going into the market, no? So when they were caught, then they actually tried to sue the Ghana FDA so I think the cause was, you’re now enforcing your law? How can that happen? You never did that in past. So in this case, I mean, it looks like it actually helps to strengthen the hand of the Ghanaian regulatory. It also does something to the reputation of Indian drugs in general in this country.
And that cannot be – you know, at one point, it has to get back home that other manufacturers in India start worrying that they’re always seen as the bad guys. They always are associated with low quality wherever they go. That cannot be good for business. So I think what starts out as protecting business interest, in the long run, undermines business interest. And that gives me a little bit hope that I think at one point, there will be sufficient wakeup call to not only the regulators, also the – I’d say the more responsible manufacturers to say we have to stop that and we have to be a bit more serious about actually sticking to our own rules because the Indian Schedule M – this is the Indian GMP regulation – is not that bad. I mean, we had some years ago a WHO pre-qualification expert assess it and compare it to the WHO GMP. So it’s not that specific in certain points, but with a few amendments, a few technical instructions, it is pretty much similar to WHP GMP at least in the core points for drug safety.

So it’s an interesting dynamic which I think may in the long run play out positively because it really undermines the reputation of the Indian industry like you have seen in the food sector, the same happen to the Chinese, you know, with the American housewife is worried about the Chinese food products.

MR. THAKUR: Can I just – I think that the point that you make about the Indian standards, Schedule M, I think it’s a really important point. I think it’s important to understand that. I think at the conceptual level, right, it’s very similar to the regulations, WHO GMP standards.

But you have to look at a document like that in the cultural context, you see. I think that you can be prescriptive about (CGMP ?) in the United States and expect companies to do a lot of operating procedures based upon a concept that’s articulated in CGMP. The problem in India is unless you are prescriptive, which is where the Schedule M actually is very, very poor, right?

There are certain areas like, for example, when you send an inspector to inspect, you’re essentially telling them that you’re comparing the standards of the company that has been inspected against an established regulation. If the established regulation has holes in it, then you really can’t hold the inspector accountable for holding it against it, the regulation that you have. In a country like India, I think it’s critically important to have very prescriptive policies because of the culture, otherwise, you know, people will find ways to work around that, and that’s the challenge.

MR. BATE: One of the reasons I was interested and mentioned that Harry put me onto this paper by Preston Mason from – or poster from Preston Mason at Harvard and also Harry’s anecdotal examples of his patients is, as my stats professor used to always say – and I’ve bored this audience before with that – is the plural of anecdote are not data. But, on the other hand, people always ask, where are the bodies, right?

And also, from the research that I did early on in this, when I first came across the issue of poor quality medicines, whether they were falsified or substandard, it was because doctors working on malaria or HIV in Southern Africa were starting to be
concerned that patients weren’t responding. So what starts out often as just anecdotal data from individual doctors, it drives inquiry and the development of data.

So one of the reasons to continue to go back to—and, obviously, I’m delighted that Harry could take part today is that we simply don’t know how many people—it could be just a handful or it could be thousands of people in America that are being affected by this. We just don’t know, and it appears to me that the data aren’t particularly—aren’t particularly good.

OK. We’ve got about 45 minutes. I am going to now open it up to the floor. I already have at least one question via the Internet, but since you’ve bothered to come here, you get priority. So who wants to ask a question? We have a microphone. Any questions? If not, I will ask this question. Right. OK. OK. Yes. Go. Go ahead. Fire away. Use the mike so that everybody can hear. Thanks. You know the drill.

Q: (Inaudible), AEI. So you have mentioned about the batches coming out and you said, you know, they were sort of average 95 percent API. But you have—let’s say you have a few good batches that are 99 percent and some bad batches. Do you see that—and this is for the local market. Do you see that the marketing of these products is segmented as well? So does the manufacturer, let’s say Ranbaxy, know that it’s selling the good quality products in, let’s say, the high income area so that, you know, the reputation effect stays, you know, people still believe that Ranbaxy is a good manufacturer? And you see that the lower quality products, as those being, you know, sent to rural areas or lower-income neighborhoods, where people are less likely to report problems?

MR. THAKUR: In India, you mean specifically?

Q: Yeah.

MR. THAKUR: No. I don’t have any data to actually—you know, that’s a good theory but I have no information to sort of, you know, confirm what you’re saying. That would be very devious if somebody did that.

MR. BATE: I have this question: FDA has required Ranbaxy to hire surrogate quality control experts to help the firm come up to US standards of production and data collection. Is that helping? The agency has advised other Indian firms that have had adverse observations, like—(inaudible)—surrogates? Any comments? Is it helping?

MR. THAKUR: I don’t know. I mean—you know, I’ve left that company, you know, almost eight years ago so I have no insight into what they’re doing in house. But, I mean, one can only look at, you know, the outcome. You see, clearly, you know FDA has told Ranbaxy way back in 2008 to go hire outside experts, but they had a massive recall of Lipitor last year, right? So, clearly, you know, just looking at outcomes, you know, it doesn’t seem to be working, but, internally, how long does it take for you to fix the problem, I have no visibility into any of that.
Q: Hi. Katherine Eban with “Fortune” magazine. Roger, I wanted to ask about the Preston Mason paper, and I actually met with him. And a point that he makes is that the Lipitor that he tested, the generic Lipitor, most of those samples are totally ineffective, and yet, they would still have a passed FDA bioequivalent standards. So he makes a point that the FDA’s standards are totally ineffective and that you have to look at – basically, you have to use mass spectroscopy in order to detect these impurities that render these drugs ineffective.

So I’m wondering with that example in mind, what might that tell us about the way that the FDA is vetting these generic drugs and whether their standards are just, you know, ineffective for measuring quality.

MR. BATE: That’s a frightening situation because I haven’t spoken to Dr. Mason. I don’t have an immediate response but it strikes me that the system for assessing heparin was incredibly basic until 149 Americans or however many died as a result of bogus heparin coming from China. It wouldn’t surprise me that we wait until, you know, Harry starts reporting in the “Lancet” or “New England Journal” that he’s got patients who are dying possibly because of medicine that before you see any action.

I mean, it strikes me that if you have – and you can – others please comment – if you have products which are known to have impurities that make the product ineffectual, let’s call it that, that are passing FDA guidelines, that’s of extreme worry to all of us. And I have no better response than that. I know very little – maybe – Harry, who is the cardiologist here, could think this through as to what we should be demanding. Is it the standards of approval before?

I guess the first question would come to mind for me is, were these products assessed by the FDA – and I’m sure they were? Did they measure the impurities when they assess them? No, not at all? Do we –

Q: Can I have my mike back?

MR. BATE: Sure do because I think it’s important. This is a very, very important point.

Q: Yeah. My understanding is that the – if I understand Dr. Mason’s findings correctly, that the bioequivalence testing would not have identified or turned up the impurities which were rendering the drugs ineffective. And the impurities were the result of manufacturing shortcuts.

MR. BATE: My question is slightly more precise in the sense that did the manufacturers have very low impurities when they got approval, because he’s sampling from within the field, of the post-approval products. And this is part of my thesis is that most of the companies we’re dealing with can make good quality products. They don’t
choose not to, but they cut costs after it’s been approved. Now, maybe Danish address and Harry can comment.

MR. SEITER: I have like a little bit warning flag here to see. We are talking also about a controversy between a brand name manufacturer, who, of course, has a very strong commercial interest to fight all generics that are taking away market share. So if I hear these kind of things that say, OK, it may be that impurities, although, of course, you know, by definition are relatively small concentration that they are kind of sticking so strongly to the receptor that the original drug doesn’t work. And, yes, in bioequivalence testing, you don’t measure impurities. Am I right? So you only measure whether the active substance is going basically at blood level curve similar to the original drug so you would never capture this.

But, as I say, I’m a little bit skeptical, but this is going to play out anyway because, you know, both sides, the generic manufacturers as well as the originator drug will probably, you know, get their scientists up and – (inaudible) – it out.

MR. BATE: As far as I know, Preston Mason does not work for Lipitor. I mean, does not work for Pfizer. I mean, he works at Harvard Medical School. No. But I mean, that’s – we’ll find out how significant it is.

MR. THAKUR: I’d like to hear what Harry says before – I have a couple of things to say, but –

MR. BATE: Harry, any responses?

MR. LEVER: Well, I think if – I did speak to Dr. Mason. I’m not a biochemist but what he said was the way the molecules were altered in some of the samples that he would expect that it wouldn’t have the – it wouldn’t lower the cholesterol.

So, you know, again, I’m – that was the first paper that I’ve – or presentation that I’ve ever heard that things to be altered like that. But I think if the molecules are altered, you’d be concerned about it. And I think you need – I think it needs further work. I think we need to look at those sorts of things because, you know, is it that the – when it comes out of the factory, are all the molecules made the same? Is that part of our issue? Is it impurities that are put in that do something to be absorption separate from the way the molecule itself is constructed? My understanding was the actual construction of the molecule was different, not just impurities in the drug.

So I think – you know, I think the whole process needs to be kind of relooked at, and say, where are we getting these problems from? You know, I think, clearly, there are issues. As we said, we don’t know how bad these issues are. There are, you know, minor, again, anecdotes, but, you know, enough of them that I’ve been concerned about it.

And I think – I’ve talked to other cardiologists, other physicians, and, you know, when you talk to them, and you say, you know, I’ve had trouble with Metoprolol
Succinate. What trouble have you had? You know, I’ve had some. And, as a matter of fact, when I was taking my blood pressure – this is another doctor you’re talking – my blood pressure wasn’t under as good a control when I was taking that other preparation. And then I switched and now it’s better. But, you know, we’re all kind of sitting in our own island, you know, we deal with our own patients, and it isn’t until everybody starts talking that, yeah, we’ve had a few of these and a few of those that we need to start thinking about it.

But I think when we start – again, I can’t emphasize enough, there seems to be a problem through the drug industry in general where we never used to hear about problems at all. You know, we would kind of – maybe we were foolish and maybe we missed it, but we always sort of had a feeling that the drugs were fairly consistent and there was a whole deal about batch to batch consistency. And I think we’ve kind of lost that in this day and age where we’re trying to save money and cut costs.

When you – you know, one of the problems that’s been with drug manufacturing is metal shavings in liquid injectable drugs. Well, why do you get the metal shavings? Because probably the machines are wearing out, they’re letting them run a little longer than they should before they retool because when you retool, it costs money. And so – you know, it may be that we need to – there has to be rules about when do you change the machines and how much metal are you allowed to have in a sample before you have to take it out of production? And I don’t know that people are doing that. I mean, I don’t work in that business. We sit here on the end of it but that’s something you begin to wonder about.

MR. THAKUR: That’s precisely what I was hoping Harry would say because I think the economics, you know, when it comes to generic drugs, are partly the drivers of this, you know.

So if you look at how the approval process works, typically, when you have the initial approval, you have as close as possible to the original formulation, including the excipients and intermediates. The moment the drug gets to the market, the generic manufacturers goes through his process of filing variations. Variation could be to get to a different site. Variation could be to change the process. Variation could be to add another – or substitute, or swap-out an excipient or an intermediate.

I mean, I know for a fact that in one particular case, there was this drug that actually had a matrix of essentially eatable wax it was suspended in. And, you know, after a period of time, after the initial 180 days, the manufacturer essentially sort of substituted that with soybean oil. Well, guess what? Soybean oil, you know, essentially – it goes bad. It has problems with stability. It manifested itself in problems with stability. And the manufacturer knew this. And, you know, whether the FDA actually signed off on it or not is a completely different story.

But I think that, clearly, if you look at what happens when you have new drug approvals, because they’re tested in a very small population in clinical studies, the FDA
requires commitments, which are called phase four studies, post-marketing studies, to follow these drugs over a longer period of time to see how these drugs are actually working in the market. We have nothing of that sort because we take it for granted that if a swap works in the lab, if the dissolution is what you know, is identical to what we have seen with the original formulation, it is supposed to work exactly the way physiologically when you take it.

And, you know, Harry’s anecdotes are a testament to that that they don’t. And we have no mechanism to sort of follow that out and then see exactly what is happening in the market when people switch from the brand to the generic. And, you know, I mean, you could argue on both sides. As Andreas said, argument could always be you know, the companies trying to protect their formulation because they make money off of it. But we don’t have data. We just don’t have data to say one way or another at the moment.

MR. BATE: Very interesting. I should stress that I did invite the FDA to be here. They didn’t reject the idea. They just the people that we wanted to have here couldn’t make it today, probably because they’re all traveling.

But I wanted to bring up – actually, if there’s more questions, I’ll bring this up towards the end. Yes. The gentleman here.

Q: Hi. Claudio Lilienfeld from the Podesta Group. I was wondering how much of an effect, if any, the general pricing pressures within India have on this, meaning with public health spending being relatively low still and you cited that, Mr. Thakur, that are the firms also under pressure because their margins are so low within India that simply to serve the global market, if they’re serving India’s market as well, this is leading to some of this corner cutting?

MR. THAKUR: It is. I mean, I think the price pressures are actually a really important, you know, factor that plays into this Indian economics. And the outcome of that is that there are two different standards of drugs that are manufactured in India. There is a certain standard that’s followed for drugs that are dispensed in India and shipped off to Ghana to Latin America which are of a lower standard than what is shipped to the United States. So what gets sold in the US actually is of a higher standard than what is sold in India. That’s the unfortunate reality of how the market works. Is it a spillover effect because of the local market? I believe that is but I have no data to actually substantiate that comment that I’m making here.

Q: Each – Barry Leven (ph) – each one of these problems, the purity of drugs, the standardization, is one batch as same as another, I mean, every one of those is a very difficult one to follow and solve.

The other – but the question also that nobody’s mentioned is, after market survey – one of these sessions before the summer I met some fellows who have a company – Americans – who have a company in India where if you get a drug in India, you can just on an app send in the batch number and they’ll tell you whether it’s real or not. But in
this country, we’ve stayed away, obviously because of the cost and the difficulty of the aftermarket. But it seems to me that that’s critically important to do on a sampling basis because an awful lot could be found out about that. The question is do you do it with a patient, will the patient report what they want? Do you do it with a physician? The patients don’t go to them. But, I mean, it’s an area that I don’t think we can just let go, laissez faire, that if the physician happens to report something to the pharmaceutical company about that he found that he thinks there’s – is the only way of knowing, I mean, it just is totally inadequate, it seems to me, especially with the level of drug usage and the generic issue in this society.

Do you know anything more about that Indian company and where it’s – American company that operates – I can’t remember its name.

MR. BATE: The company is PharmaSecure, which is a U.S.-Indian company. They’re labeling, if you like, their products for identification that this is a real product made by the manufacturer on a label. So it wouldn’t deal with the issue of quality control of the product itself. It just says, if it says, Pfizer or Ranbaxy on the label, it’s actually made by them because you basically call up a telephone number and it checks that it is there.

So there were systems like that being put in place, and Nigeria and Ghana have different companies working on this. And they’re very useful I think for identifying going after falsified, fake, counterfeit products. But they – I don’t see how they would work in this space because all they’re doing is identifying that the product is real, not the quality of the product.

But you say that we shouldn’t let this open to laissez faire, and I suddenly realize that, you know, this is AEI. We should address what the market response should be to this or could be to this.

One of the most interesting things for me is that – is how responsive or how innovative industry is actually allowed to be in this area. And I’m certainly no labeling expert. But there’s very limited information you get on a pill pot when you get a prescription drug in the United States. If you’re in the U.K. or you’re in most countries – most other countries in the world, you would get a blister pack with a cardboard box inside with aluminum packaging with individual pills that you push out. You can have a lot more information.

I’m wondering if innovative companies – I don’t necessarily mean that they are brand companies, innovative companies, but innovative generic companies would be able to label their products so that you could identify exactly where the product was made, where the ingredients were sourced from, and, consequently, that you have avoided either locations or companies that are either on a black list or you’ve only bought from a white list, say.
And the reason I – you know, we know more about where we get our milk from than we do our drugs, a hell of a lot more. I mean, you know, you look at most food labels, you know exactly which country it’s come from, or you may not know the cow that the milk’s come from but you know the farm that it may have come from.

You buy any drug in the United States, you have absolutely no idea where the medicines come from. Often, it doesn’t – there’s zero information. Even in – you know, other places, it will say – it might say manufactured in country X or city X, but it doesn’t tell you where the ingredients are from.

I’m wondering if the labeling restrictions that the FDA has, historically for good reason, actually restricting the ability of companies to be able to put information on products that would help them differentiate not in a way that’s to do with, you know, the formulation of the product, but in terms of identifying that they’ve avoided certain locations or they have confirmed them, rather than being negative, being positive, that they had said that these are made in these locations, and we know 100 percent certain that the ingredients came from these locations.

I’m just wondering, you know, where the – you know, if anybody else wants to comment on this, but that would seem to me the positive way that a business response could be to this, but I’m just wondering if the labeling restrictions are so restrictive that you can’t actually follow that line.

Andreas, you see – advised countries, and, you know, probably generally to see what they can do to follow kind of FDA guidelines but –

MR. SEITER: Frankly, I don’t know much about the FDA guidelines and to what extent they’re restricting adding additional information on it. Technically, it’s certainly possible. I mean, in the registration file, you have details about where the various ingredients that go into the drug are being sourced because in good manufacturing practice, as the manufacturer of the pill, you have to also basically provide the data for the active ingredient.

So I think, if you look at that, the information is available when the drug enters the country, but it’s not communicated to the consumer. It could easily be. I mean, you can, of course, use like micro, you know, text that someone put anything on it. But, I mean, the question is to what extent – or it could even use this SMS technology or something linked to – which takes you to a website where you’ll find everything you want to know so possibly, technically, absolutely. Whether it’s legally possible in this country, I don’t know.

We are suggesting – after, when we discuss with regulators to think about this track and trace technology, is this something you could make a regulatory requirement. Obviously, that has implication, when you source from like 3,000 different manufacturers worldwide, you know, and you want everybody to comply with it. In particular, if you’re a small market, you don’t have the bargaining power to do that.
My question to you about the Indian law on track and trace, which I think it was supposed to be implemented, so that it really only helps identify when you have a pill pack in your hand, you can track back to where it came from. It doesn’t say whether it’s good or bad quality, but it can – it makes it a little more likely that it is good quality because at least the maker of the pill knows that they can be traced back.

MR. THAKUR: I don’t have a lot of information about the implementation of pedigree within the Indian context. I know there have been a lot of discussions about this. I think that the health secretary has spoken, basically saying that they want to have the pedigree of the drug.

But as Roger said, I think the challenge here is all of the track-and-trace legislation and pedigree systems track from the point that the packaging is made, right? It’s from the time that the drug leaves the warehouse and they track the pedigree of it in the market until you get to the consumer. What we’re talking about here is prior to that aspect. You’re talking about the manufacturing aspect of it, where it’s coming from. So I think, clearly, there’s an opportunity to –

MR. LEVER: Roger. Roger.

MR. BATE: Yes.

MR. LEVER: My understanding is that two weeks ago, the president signed a law that will require track and trace. Now, they say, to be fully implemented, it could take 10 years. And it wasn’t clear to me from the newspaper accounts what exactly is going to be required, even starting now. But there is some movement, it sounds like, that track and trace is going to go into effect. I don’t know if anybody there has more information about it, but it was about the 17th or 18th of November he signed the bill.

MR. LEVER: Our most well-informed journalist has this information, Katherine Eban.

Q: My understanding is that the track and trace law, which is just long overdue really deals only with the distribution system, and it’s intended to address problems of sort of rogue wholesalers and middlemen, but really, it sort of picks up from the moment the drug leaves the manufacturing warehouse so that doesn’t necessarily deal with, you know, components within manufacturing. I mean, I think that it wouldn’t – to Harry’s point, you know, it’s a movement that is beginning but I think that in terms of a lot of the discussion that we’re having here today, it wouldn’t address – you know, it wouldn’t get into the supply chain of where is the API coming from, how are the finished doses being made, what are those processes? It really picks up after that’s already completed.

Q: Thanks. Richard Tren, Searle Freedom Trust. Roger, you’ve used Raman spectrometers, and I know that some like NAFTAC (ph) is using it. Is it – would it be useful for pharmacists if you went to the – you have a (CVS ?), could they have one?
Would that be a practical way of determining whether or not the quality of a generic is
good at the sort of point of sale?

MR. BATE: It’s an interesting – it’s an interesting question. I think that soon for
things like this, for the iPhone there will probably be an app to identify a very limited set
of drug samples. So, for example, if you’re on a statin, the lights in – you wouldn’t get a
laser on a phone, but the high-quality lights that you can get from these phones might be
enough to – if it’s just for one or two products, you might be able – I imagine we’ll get to
that stage.

But using a Raman spectroscopy, you can very effectively identify products that
are falsified. So if they have the – if they have zero API in them and they’ve got weird
excipients in them, you’re going to spot that immediately within five seconds. The
problem – and that’s why I focus more and more on substandard medications rather
than falsified ones because falsified medicines are a big problem in the United States and
certainly around the world, but there are more tools to address it, more – because you’re
dealing with criminal elements and there’s an obviously activity which is outside even –
even of countries that don’t have anti-falsification of drugs, they all have fraud and other
laws that they can apply. I think the international community is ponderously but it is
moving in the right direction of combating this.

Substandard drugs are harder to identify with those kind of technologies because
assuming they’re made by the legal manufacturer and they are – they have roughly the
right, you know, spectral mix, it’s very difficult to be able to spot a truly bad product
from one that’s probably within specification but not quite along the lines of the perfectly
made product to begin with. It might raise flags and they can certainly be used, but you
would be rejecting – if it’s failed, and you, therefore, didn’t give it, you’d be rejecting
products that might work and that false negative would be a huge problem for
pharmacists and others.

So I don’t think it has – I don’t think unfortunately it can be as useful in
identifying substandard products. So you don’t have the technology. And you also find it
very difficult for governments to address this. So in action against sub-standards it’s the
biggest concern I see out there in the global community. and the lack of being able to
deploy certain technologies is just one manifestation of it. Yeah.

Q: Roger Murry with Akin Gump. I represent the Certified Importer Program
Coalition. And they have put together a proposal looking to help consumers identify
supply chain issue, identify the best manufacturers and importers. And FDA has a
proposal before them. It builds on language in FDASIA Title Seven. I’m happy to talk to
more about it later.

So we’re working to help FDA understand the resources available to it that highly
compliant importers can bring to the table to help consumers know, just looking at a box,
where did this come from, where did the active ingredients come from, where did the
excipients come from throughout the entire supply chain.
MR. BATE: I mean, that’s really interesting. I mean, I imagine one of the biggest concerns – you might want to respond. I imagine one of the biggest concerns about this is cost. And thinking again, in some respects – and this is unfair to the drugs industry – the drug industry is about 20 years behind the food industry in terms of – I remember all the protestations – we can’t separate out genetically modified soybeans from other types of soybeans. A lot of those criticisms were real and were unnecessary to do it in the first place. But when it became an economic issue that there were enough consumers that were going to demand this type of product over that type of product, business said, well, it’s in the interest.

I mean, what are the costs – what are the potential costs to businesses? And are they – are they going to be able to advertise themselves and hence increase their costs to supplies? In other words, will you get to the stage if you’re thinking this through, as I imagine you have to be, that a patient can go to – will get a prescription from their doctor that says – it doesn’t just say, you know, brand name, because it could be – but these specific generics I’m happy to take. Could you get that level of specificity on a prescription? I mean, that’s the kind of thing you’d need if the patient is prepared to pay more but to identify these products.

Q: I’ll say that the higher compliance supply chains exist. So it’s about helping them identify which drugs are coming from those supply chains. And I think as a program like this involves and consumer awareness increases, I think that companies participating in a program like this run by FDA would be looking for opportunities to distinguish themselves.

MR. SEITER: I’ve been obviously thinking long and hard about these issues and I think there is no shortcut, even with all the advanced technology – I mean, technology can be very helpful in, you know, identifying, measuring and so on, but still, you need to know what you measure.

If you look at this Atorvastatin case, yeah, that might be that it is a new discovery that even regulators didn’t know so far that there is this particular impurity that interferes with the actual workings of the drug so that given what you have in current GMP standards, and they are called current GMP, CGMP because they change all the time, so I think this is where it all boils down to that there is a CGMP which next year will look different than this year and it may be amended by something about impurities of Atorvastatin that then the generic companies will adhere to and they will be fine. I don’t think there is anything against that that generic companies would go away or under particular pressure and so on, in particular for these older drugs that are mass market essential medicines used by most people in developing countries, that is largely a generic company’s business and we need them.

But I think the way down over the next decade and so on is going to be a more – a globalization of regulators, where the weaker countries have closer links to those with stronger regulation. Even the stronger countries like EU, FDA, Australia, Singapore,
so on, they start working together. As we speak actually today – tomorrow is a meeting in Amsterdam of heads of regulatory agencies of the developed countries, including the BRICs, so India, may be there; Brazil certainly is there. I think, yeah, Singapore, China is attending usually. They are talking right now about closer collaboration, you know, maybe a common platform for data exchange because they can’t handle it anymore. It’s so complicated. We have so many drugs that each of them may have their own very specific issues, what you have in Atorvastatin may not be the same issue in Simvastatin, which may be, you know, harmless in terms of impurities. Who knows?

All the things – it goes like five layers deep under the surface of what we see and only there you can really solve the problems. So I think the way forward is that regulators have to pull their resources globally, that we need these global track and trace systems, and global, you know, visibility of what’s happening in the supply chains that we have to use technology in terms of, you know, IT for data mining and communication technology so that we see in one place of the world if something has gone wrong in another part of the world, because it’s the same drug coming from the supply chain that is dispensed here and there.

And so I think that’s the way we are working. I mean, as an institution, we are currently, for example, you know, providing funding, which, again, comes from donors, Gates Foundation, DFID; actually the US government is in the process of providing some funding for that because they also see that their AIDS and malaria treatment programs are threatened, of course, by drug quality issues, in strengthening and creating networks of regulators. Not every country can have a regulatory agency that can deal with all of that so we have to really invest in the collaboration here.

MR. BATE: And just, if you could just go over that in slightly more detail. So, for example, I know there’s like an East African group. There’s a West African group. I mean, are there any parts of the world where they are not even contemplating doing this or is this universal now?

MR. SEITER: I think it’s universal. I mean, as I said to you, you have it at the global level between the developed countries. You have that level. Then you have already ongoing collaboration in Latin America. You have APEC collaboration.

There are some places where it’s not yet happening. I mean, in Central Asia there’s no collaboration that I know of at least. But what we are doing is we are encouraging. Whenever we talk to regulators and say, you’re not alone with your problems; everybody has these problems. And you can’t imagine how huge these problems look like for a small Central Asian country that is particularly exposed to organized crime and to all kinds of, you know, attempts to bring – smuggle in drugs of very questionable origin. It’s simply they’re absolutely not equipped for that.

So I think, yes, we will see this. Clearly the trend goes in the direction that they will collaborate. The sovereignty issues, they can be resolved by retaining the decision making power in the national agency, but all the technical work in terms of assessing,
and, you know, doing the scientific background checks, that can be pooled. You can sit together with experts from other countries, look at the same data, then still make your national decision. So I think this is the model that we are heading towards.

MR. BATE: Harry, I’m going to come to you for a final comment so that you can sign off and go and deal with our patients because I know you have to. So any – thank you for joining in today and giving us your, you know, very interesting examples. Is there anything you’d like to leave us with?

MR. LEVER: I think that we need to look more at this track and trace so we know where things come from. And I think that – and I also think that we have to realize that people, when they’re sick, they need good drugs and we have to figure out innovative ways to make certain that we can do it cost effectively and make sure that what we’re giving our patients is high quality. And I don’t think we should stand for less than that.

I think that we need – maybe we need more standards through the industry that have to be decided upon. If you’re going to make certain drugs, you have to meet these standards, and I think that anything less than that isn’t so good. I think we need that kind of level of – you know, you can’t be making it in your basement. You have to be making good quality. If you’re going to have a drug company, you have to meet certain standards. And maybe different countries that are in – you know, the major countries in the world, through the U.N. or through – whatever – World Health Organization, you have to adopt standards, and if you’re going to become a drug company making things, you have to meet those standards.

And I think that – you know, a couple of years ago, the FDA was talking about collaborating with different countries to use their inspectors, you know, England and France and Italy, you know, Germany, so that we wouldn’t redouble the inspections. We would sort of dole them out to different countries. We would understand that certain countries could inspect the way the FDA could here and maybe we should do more of that. And so that we can spread the inspectors through the world better than we do now. And I think that’s important.

MR. BATE: I agree entirely. The one thing I’d be interested, final thing for you to comment on, you’ve mentioned it; you have been forthright in your statements about some of the problems that you have encountered. You know, the plural of anecdote may not be data, but the more and more anecdotes we get together from doctors, and in your case, cardiologists, the more evidence there will be out there. So what can we do to help you and what do you think you can do to get more – if you like, more cardiologists and other fields of study, but yours is –

MR. LEVER: I think that we need more publicity about the issue. I think if you talk to the average – I got interested in this purely by accident. I was driving to work one day in 2007, and listening to NPR, and I heard about all this importation of food and drugs from China. I didn’t know about it. And it became – I started doing Google searches and I find all these companies overseas making drugs that I knew nothing about.
And then I started noticing – you know, with the heparin situation, I was concerned that summer before there was announced that the heparin was contaminated, I was a little suspicious there was something going on but we couldn’t prove anything.

But I think that if you talk to most doctors, we’re not aware of what’s really going on out there. I mean, we write a prescription, we assume that it’s OK, and that’s it. But when you start talking among yourselves, then you hear these stories. And I think that we need more information out there about these issues, about where there have been problems, and we need to – you know, we don’t want – we have to be very careful at the same time we don’t raise unreasonable alarm. We don’t want to – you know, because most drugs are probably OK. But there are ones out there where there are potential problems so we have to – our information has to be good.

And I think that the – the other thing I think is that the professional societies need more knowledge about what’s going on in America, the Heart Association, oncology and cardiology, these organizations that directly deal with physicians, they also need to be in the loop, and they haven’t so far done that. And that’s an important link where that’s where we get a lot of our information from. And I think that they need to be made aware about of what the issues are out there, and when there’s bad quality, and which manufacturers maybe we shouldn’t be relying on, and things of that sort. I think they need to also get involved in that.

And I just think that the problem has also been – you know, the FDA, we haven’t – their websites are so complicated, and trying to get information off that website is hard, you know. And so, you know, I rely on my Google searches. You know, isn’t that amazing what Google does for you. You can find out an awful lot. And that’s where I, you know, find out lots of things. And I think that they pick up – Google somehow picks up a lot of this kind of stuff, but I think that the physicians need to be made aware that there are problems. And then you get information back because what we would send in to the FDA, somehow we have the feeling gets lost, you know. But we need a better reporting system where when we recognize a problem that we can report it and be sure that it’s going to be dealt with.

MR. BATE: Thank you very much. Dinesh, do you want to give a final wrap-up?

MR. THAKUR: I think Harry said it all. I think that we just don’t have enough data. I think what we’re seeing here are anecdotes which I think are the tip of the iceberg. We just need to define, you know, the problem a little bit better so that, you know, we can come up with better measures to try and address that.

Clearly, I think that, you know – I mean, I can see the problem. I think Harry sees it in his practice as well and so does Andreas. I guess the question is: how do we define it, where are the resources to try to address it, and what is the process that they go through trying to get to where we need to go? I just don’t know.
MR. BATE: My life’s work. Thank you all very much indeed for coming, for watching online. And if you have further questions, throw them at me and I’ll follow-on them on to Dinesh. He may or may not answer. I’m sure he will. He’s very responsive.

And it’s been a pleasure to host you here at AEI. And I hope we see you here again for another event in the near future. Thanks a lot.

(END)